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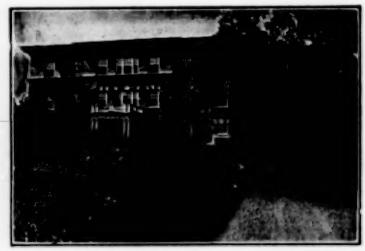

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The Journal of Nervous and Mental Disease

Vol. 119, No. 5 MAY 1954 Serial No. 869

HOWARD CHRISTIAN NAFFZIGER

May 6, 1884

He is complete in feature, and in mind,
With all good grace to grace a gentleman.
Shakespeare: Two Gentlemen of
Verona 11C 1595.

It seems only yesterday that members of the University of California School of Medicine honored Dr. Naffziger on his sixtieth birthday. The May, 1944 issue of the JOURNAL OF NERVOUS AND MENTAL DISEASE was dedicated to him.

Dr. Naffziger joined our faculty in 1913; became Professor of Surgery in 1929, and Professor of Neurological Surgery in 1947. Since 1951 he has been Professor Emeritus. But retire? Not he! He did not bury his vast experience and skill; he did not retreat to the country to breed horses or to raise chickens. In 1951 he went on a world tour, lecturing and operating in Greece, India, Formosa, England and Pakistan. He was the first to operate on a pituitary tumor or intervertebral disk in the Philippines. Earlier, in 1946, he lectured in medical schools in Poland. Wherever he goes, he is an honor to American Medicine, and our best Ambassador of Good Will. The University of California conferred on him a B. S. degree in 1907, and an M.D. in 1909. In 1952 he was appointed Regent of that University. He knows well the School of Medicine with its woes and needs; like a true Regent, he speaks with authority for it—and his voice is heard. He is President of the American Surgical Association; Senior Civilian Consultant for Neurological Surgery to the Surgeon General. He is on the editorial board of no fewer than eight leading medical journals; member, consultant,

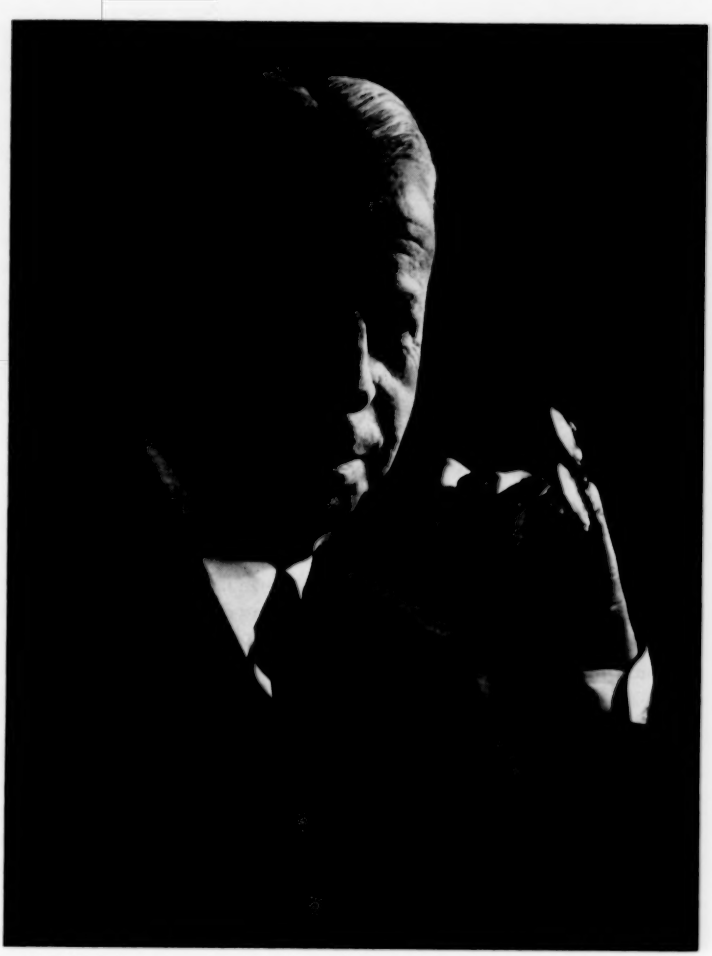
chairman, president here, or advisor, trustee, director there. If not on some official mission in the U. S. A. or abroad, he is in the hospital seeing patients, or operating, or at his desk writing, or answering mountains of mail. And yet he is never too busy to treat his patients and colleagues with the utmost dignity and decorum. Presenting a neurosurgical problem to him, I like to accompany the patient to observe Dr. Naffziger's meticulous and skillful technique of examination. I always learn something.

Like all true physicians he is intrepidly guided by the maxim: *Salus aegroti suprema lex*. He is impressively critical, cautious and strongly adverse to any drastic—diagnostic or therapeutic—surgical procedure which may harm the patient. He is not motivated by curiosity. He would rather postpone a diagnostic decision than force one. In his critical attitude toward the indication of operative procedures he should be an inspiring model for the younger neurosurgical generation. Unfortunately, of late there has been a tendency to enlarge the indication for surgical procedures. Untempered by fine critical judgment, this can prove hazardous and harmful. Dr. Naffziger's entire life is dedicated not to please any one person, but to serve a cause—the cause of the sick, of the school, of the nation. He works for the greater glory of surgery, but never for the greater glory of Naffziger. Doctors and laymen alike seek his advice not only in medical matters, and value it since it reflects ripe wisdom and supreme common sense.

Hughlings Jackson said that there is "nothing in the world to compare with domestic happiness," and it is from his unclouded domestic happiness that Dr. Naffziger draws his unyielding strength. In his all too few hours of relaxation his interests lie in his huge boxer dog, Bourbon, in a friendly game of golf, in watching pugilism on the neighbor's TV and playing dominoes. He has an absorbing passion for dominoes, and is never without a special set in his brief case on all his travels. In the summer, at his cabin in the high Sierra, he sagaciously presides over a family group of fifteen, including his wife, three daughters and their husbands, and eight grandchildren. Here he is chief laundryman, dishwasher, fisherman, hunter and hostler extraordinary.

It was Dr. Naffziger who inaugurated by transplantation from the University of Freiburg to the University of California. Dr. Harvey Cushing advised me in those troubled days, and when he heard that I had landed in San Francisco wrote me: "You could not find a better man than Naffziger." During all the eighteen years of collaboration I have felt how right Cushing was.

ROBERT WARTENBERG, M.D.



Howard C. Naffziger.

NOR-EPINEPHRINE-LIKE AND EPINEPHRINE-LIKE SUBSTANCES AND THE ELEVATION OF BLOOD PRESSURE DURING ACUTE STRESS*

DANIEL H. FUNKENSTEIN, M.D.
LYDIA W. MEADE, R.N.

Using the cardiovascular system as an indicator, Hickam, Cargill, and Golden (22) found that students reacted in three different patterns in response to psychologic stress. The authors used the cardiac output, blood pressure, and the pulse as measurements, and from these data calculated the peripheral resistance by the method of Aperia (1). Two of the patterns were associated with an elevated blood pressure, and the mechanism of each rise was different. In one of these there was associated with the rise in blood pressure, a decreased peripheral resistance, and increased cardiac output and an increased pulse rate; whereas the other blood pressure rise involved an increased peripheral resistance, an unchanged or lowered cardiac output and a lowered pulse. Goldenberg, Pines, Baldwin, Greene, and Rog (18) studied the effects of nor-epinephrine and epinephrine. They found that the infusion of epinephrine produced the following pattern: increased blood pressure, increased pulse, decreased peripheral resistance, and increased cardiac output; whereas the infusion of nor-epinephrine resulted in: increased blood pressure, unchanged or decreased pulse, increased peripheral resistance, and unchanged or decreased cardiac output.

In can be seen from these two studies that when an elevated blood pressure was one of the responses to psychologic stress, at least two different mechanisms could account for the rise. These two mechanisms were similar physiologically to those produced by the intravenous infusion of epinephrine and nor-epinephrine.

We have studied psychiatric patients by means of a test of the autonomic nervous system (13) which utilized adrenergic stimulation (intravenous epinephrine) and cholinergic stimulation (intramuscular mecholyl). Following standardized dosages of these drugs on different

* From the Department of Psychiatry, Harvard Medical School, and the Boston Psychopathic Hospital. We gratefully acknowledge the assistance given us by Harry C. Solomon, M.D.

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Nor-epinephrine was furnished through the courtesy of Shepherd M. Crain of Winthrop-Stearns, Inc. Mecholyl was furnished by Merck and Company.

days, the systolic blood pressure and the psychologic responses were followed for a fixed observation period. The systolic blood pressure responses were divided into seven groups and the psychologic responses into four. The technique, relation of these tests to somatic treatments, to psychotherapy, to spontaneous changes in patients, and to asthma were reported elsewhere (11, 13, 14).

One of the striking phenomena observed in our patients during the course of the experiments was the marked difference in the blood pressure reaction following the injection of mecholyl. When the blood pressure reaction to mecholyl was classified as "marked" and the preinjection level was not reached during the 25 minute observation period, the response to electric shock was good (13). In contrast to this, when the blood pressure reponse to mecholyl was classified as "moderate or mild" and the preinjection level was reached within the 25 minute observation period, the patients usually did not respond to electric shock treatment. Further observations showed that in patients with elevated blood pressures the same two blood pressure reactions to the injection of mecholyl occurred, and that these too were a reliable index of the clinical response to electric shock therapy.

Noting the difference in the reaction to mecholyl in these two types of cases with elevated blood pressures, and the prognostic significance of this difference in relationship to electric shock therapy, the work of Hickam, Cargill, and Golden (22) in relation to the mechanisms of elevated blood pressures during psychologic stress, and the work of Goldenberg et al. (18) on the nature of the mechanisms of elevated blood pressures produced by epinephrine and nor-epinephrine, the following hypotheses were stated:

1. One type of elevated blood pressure in psychiatric patients and in healthy normatensives during psychologic stress was due to excessive secretion of epinephrine, and another type of elevated blood pressure found in the same two groups of subjects was due to excessive secretion of nor-epinephrine.

2. The mediating substances of the elevated blood pressures could be determined on the basis of the blood pressure reaction to mecholyl.

The experimental work in this paper designed to test the above hypotheses was divided into three sections:

1. Studies of the blood pressure reaction following the injection of mecholyl in psychotic and psychoneurotic patients with elevated blood pressures.

2. Studies of the blood pressure reaction following the injection of mecholyl in healthy normatensives who reacted to a psychologically stress-inducing situation with elevations of their blood pressures.

3. Experimental studies of the blood pressure reaction following the injection of mecholyl in healthy normatensives, not under stress, whose blood pressures were elevated by a constant intravenous infusion of epinephrine or nor-epinephrine.

I. Studies on the Blood Pressure Reaction to Mecholyl in Psychotic and Psychoneurotic Patients with Elevated Blood Pressures

This study was based on an original group of 121 patients who fulfilled the criteria of an elevated blood pressure. They were drawn from a larger group of 508 patients, who were routine admissions to the Boston Psychopathic Hospital, and who had been given the routine test of the autonomic nervous system alluded to above (13).

The criteria of an elevated blood pressure used were: 140 mm. Hg systolic, on at least two occasions, after the patient had been lying supine under basal conditions for a minimum of 30 minutes. The level of 140 mm. Hg systolic was arbitrarily chosen. The same level was used by Pfeiffer and Wolff (27) and Saslow et al. (29) in their studies of hypertension. No diastolic level was used, as it was known that blood pressure elevations associated with epinephrine would show little or no elevation in the diastolic pressure (18).

One hundred and twenty-one patients fulfilled these criteria, but 21 cases were eliminated from the study. They showed anxiety precipitated by either epinephrine or mecholyl, or on clinical study showed evidence of cardiac, renal, or cerebral disease. The reason for eliminating those with "precipitable anxiety" was that our previous studies had shown these patients to differ in their clinical picture and in their response to somatic therapies (13, 14).

In the 100 patients who comprise this study, there were 58 males and 42 females, with a mean age of 37.5 years, and with a range of from 17 to 61 years. The diagnoses may be seen in Table I.†

† Since these patients were chosen arbitrarily to have elevated blood pressures which by hypothesis could be due to epinephrine or nor-epinephrine, the objection might be raised that this elevation was due to age. The systolic blood pressure of the patients with elevated blood pressures ranged from 140 mm. Hg, with a mean of 151.4 mm. Hg. The 408 patients with blood pressures below 140 mm. Hg systolic showed a range of from 84 to 138 mm. Hg, with a mean of 116.4 mm. Hg. A "t" test of the significance of the difference between the means showed these to be significant differences. The mean age of the group with elevated blood pressures was 37.5 years, with a range of from 17 to 61 years, and of the 408 patients with non-elevated blood pressures, the mean age was 31.2 years, with a range of from 16 to 59 years. This too was a significant difference in ages on the basis of the "t" test.

In order to determine whether or not the elevated blood pressures could be at least partially due to the emotional upset associated with the psychiatric illness, rather than explainable on the basis of age alone, blood pressures were taken after treatment on at least two occasions under basal conditions, on 46 cases selected at random from the 63 cases

TABLE I.—Diagnosis of 100 Psychiatric Patients Studied

Dementia praecox	39
Manic-depressive	20
Psychoneurosis	11
Involutional psychosis	23
Miscellaneous	7
Total	100

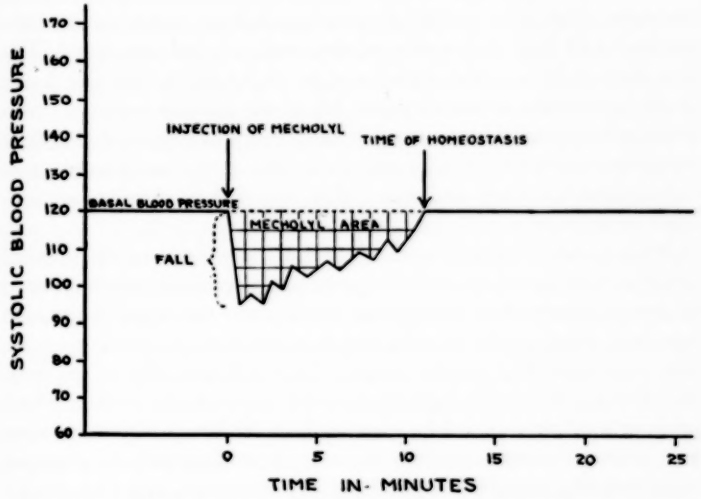

Fig. 1.—Diagram to show the method of obtaining measures after the injection of mecholyl.

II. Studies in Healthy Normatensives who Reacted to Psychologic Stress with Elevations of their Blood Pressures

Thirty-three senior medical students formed the nucleus of this part of the study. No criteria were used for their selection except willingness to take part in the experiments for a fee. They were all functioning well

which received electric shock treatment. These blood pressures were taken after the patients had received treatment, and of these 46 cases so studied, 36 had improved sufficiently to be discharged from the hospital without further treatment. In these patients, after electric shock the mean of the blood pressure was 133.2 mm. Hg systolic, which was a statistically significant drop in the bood pressure from the preshock level. The age of this group, however, showed a median of 37.2 years, which did not differ significantly from the group of patients with elevated blood pressures prior to treatment. This would indicate that while age may be a factor, it would only be one factor, and not an important one at that and that the elevated blood pressures in these cases might well be explained on the basis of the emotional upset incident to the psychiatric illness.

in school. The autonomic test to be subsequently described was administered to these students on three different occasions: the first test was performed a month prior to the stressful situation, the second test during the stressful situation, and the final test one month after the stressful situation was over. The tests were done after the student had lain supine for at least 30 minutes, two hours after the last meal.

The stress-inducing situation chosen was the night of the announcement of interneship appointments. The announcements were made at midnight. This is a period of great psychologic stress to the men involved and they feel under tension, anxious, and concerned. The tests during the stressful situation were performed within five hours of the interneship announcements. All of the students reported themselves as being tense, anxious, concerned, angry or depressed and their appearance confirmed this. In contrast to this, at the nonstressful times they appeared relaxed and stated that they felt *no* tension, anxiety, anger or depression.

Twenty-four of the 33 medical students responded to the stressful situation with elevations of their systolic blood pressures, which reverted to approximately their preinjection levels when the stressful situation was over. Prior to the stressful situation the average systolic pressure was 115.6 mm. Hg systolic, ranging from 108 mm. Hg to 124 mm. Hg. During the psychologically stressful situation the average blood pressure was 145.0 mm. Hg, ranging from 130 mm. Hg to 170 mm. Hg; after the stressful situation was over, their blood pressure averaged 114.2 mm. Hg, ranging from 106 mm. Hg to 120 mm. Hg. The average rise during the stressful situation was 31.3 mm. Hg, ranging from 16 mm. Hg to 52 mm. Hg. The average age of the students was 22.5 years, ranging from 20 years to 28 years.

The 9 medical students who did not respond to the stressful situation with elevations of their blood pressure all showed other alterations of their autonomic nervous system reaction at that time as measured by this test. One had a chill after mecholyl, three had changes induced by epinephrine which they interpreted as anxiety, and in 2 cases there was a fall in blood pressure. These 9 cases were eliminated from the study so that this group would correspond to the patients.

Administration of the Test. The tests were administered to the patients and to the medical students as follows:

After the subject had been lying down in quiet surroundings for at least 30 minutes, two hours after the last meal, the blood pressure was taken by the cuff and ausculatory method by a nurse. She then injected 1 cc. of normal saline intravenously and followed the blood pressure for 10 minutes. After a 10-minute interval, .05 mg. of synthetic

l-epinephrine in 0.5 cc. of normal saline was given intravenously and the blood pressure followed every 30 seconds for 10 minutes. (This was the basis for eliminating the patients with anxiety precipitated by epinephrine, as stated above. Criteria of "precipitable anxiety" may be found in our previous publications [13].) After a 10-minute interval, the subjects were given 10 mg. of mecholyl chloride intramuscularly, and the systolic blood pressure followed for 25 minutes. The subjective responses of the subjects were noted.

Measures. Following the performance of the physiologic tests as described, graphs were constructed from the data, with time as the abscissa and the systolic blood pressure as the ordinate. Only the basal blood pressure as a continuous line and the systolic blood pressure after mecholyl were recorded. From these graphs the following measures were obtained:

1. Time of Homeostasis: This was the time the preinjection level of systolic blood pressure was reached following the injection of mecholyl. If the preinjection level was not reached within the 25-minute observation period, it was scored > 25.

2. Area: This was the number of squares between the line representing the basal systolic blood pressure and the line representing the systolic blood pressure taken at one minute intervals after the injection of mecholyl. (On the ordinate each square represented 6 mm. Hg of systolic blood pressure, and on the abscissa each square represented one minute of time).

3. Fall: This was the difference between the lowest systolic blood pressure reading obtained after the injection of mecholyl and the preinjection level.

Figure 1 shows graphically how these measures were obtained.

Results in the Patients. The patients fell into two groups on the basis of whether or not the preinjection level of blood pressure was reached within the observation period. All those in whom the "Time of Homeostasis" was greater than 25 minutes were placed in one group known as Group A; those in whom the "Time of Homeostasis" was less than 25 minutes were placed in another group known as Group B. The average "Time of Homeostasis" in this latter group was 7.75 minutes, ranging from two minutes to 16 minutes. This was not done arbitrarily, but was done as the result of our previous work, which showed this to be a crucial variable in regard to predicting the response to electric shock (12, 13).

A "t" test showed these differences in "time" to be significant. "T" tests for the difference in the significance of the means were then run for the variables of "fall" and "area" between Groups A and B.

This showed that Group A had a greater "fall" and larger "area" than did Group B. This was statistically significant. Table II.

Comment. Division of the psychiatric cases into two groups on the basis of their blood pressure reaction to mecholyl—Group A (preinjection level of blood pressure not reached within the 25-minute observation period) and Group B (preinjection level of blood pressure reached within the 25-minute observation period)—was shown by a statistical analysis to have a high probability of representing two groups on the basis of a "t" test run on three variables. The original criteria for division according to "time" were derived from our previous work, which showed that this was a crucial variable in regard to the response to electric shock treatment (13).

Results in the Students. In all of the students under nonstressful situations, both before and after the stress, there was no basis for the establishment of two groups, as homeostasis (preinjection level of blood pressure) was established in all of the cases within the 25-minute observation period (10).

However, during the psychologic stress, those with elevated blood pressures fell into two groups on the basis of "Time of Homeostasis" after the injection of mecholyl: Group A (11 students), in which the preinjection blood pressure level was not reached within the 25-minute observation period; Group B (13 students), in which the preinjection level of blood pressure was reached within the 25-minute observation period. The "Time of Homeostasis" in this latter group averaged 8.4 minutes, with a range of from 5 minutes to 11 minutes.

A "t" test showed these differences in "time" to be significant. "T" tests for the difference in the significance of the means were then run for the variables of "fall" and " area" between Groups A and B. This showed that Group A had a greater "fall" and larger "area" than did Group B. This was statistically significant. Table II.

TABLE II.

	Patients		*Students*	
	Fall	Area	Fall	Area
Mean > 25	40.0635	93.7460	43.8182	105.8182
Mean < 25	26.7568	16.8108	20.7692	15.0769
$t =$	5.3335	10.2412	4.1685	7.8742
$p =$	$< .01$	$< .01$	$< .01$	$< .01$

Comment. It can be seen from these statistical analyses that when psychiatric patients with elevated blood pressures and normatensive students whose blood pressures were elevated during psychologic

stress, were divided on the basis of whether or not the preinjection level of blood pressure was established after the injection of mecholyl within a stated observation period, there was a high probability that here we were dealing with two different populations. A typical reaction for each of these groups may be seen in Fig. 2.

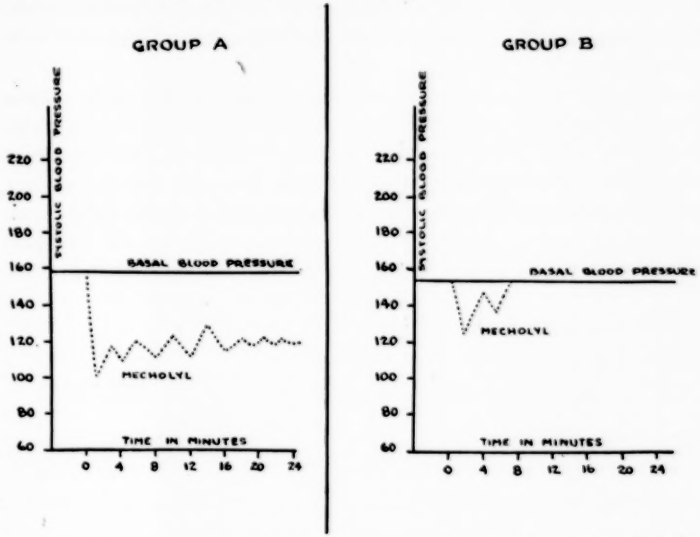

FIG. 2.—Typical reaction of each of the groups after the injection of mecholyl in psychiatric patients with elevated blood pressures, and in students who respond to psychological stress with elevations of their blood pressures.

III. EXPERIMENTAL STUDIES

Since the psychiatric patients and the healthy normatensives under stress who had elevated blood pressures both showed two similar reactions to mecholyl, we were interested in determining the difference in the mechanisms of the two types of raised blood pressure. As stated previously, Hickam, Cargill, and Golden (22) had found two mechanisms to account for elevated blood pressures found in response to stress in medical students. One type of elevated blood pressure was associated with an increased peripheral resistance, a decreased pulse rate and an unchanged or slightly decreased cardiac output; the other type of elevated blood pressure was associated with a decreased peripheral resistance, an increased cardiac output, and an increased pulse. These findings were the same as Goldenberg, Pines, Baldwin, Greene, and Rog (18) found after the intravenous infusion of nor-epinephrine and epinephrine in normatensives respectively.

From these findings, we stated the hypothesis that one type of elevated systolic blood pressure in response to psychiatric illness or to psychologic stress in healthy normatensives was associated with epinephrine, and the other type of elevated blood pressure with nor-epinephrine. The type of blood pressure elevation could be determined on the basis of the subject's blood pressure reaction following the injection of mecholyl. Accordingly, the following experiments were carried out:

Ten healthy male normatensives were studied. The only criteria for choosing them were that they were functioning well in college, were willing to take part in the experiments for a fee, and that on at least seven occasions their blood pressure remained below 130 mm. Hg after they had lain supine for 30 minutes, and that after intravenous saline had been given on at least three occasions no rise in blood pressure occurred. The average age of these subjects was 23.1 years,

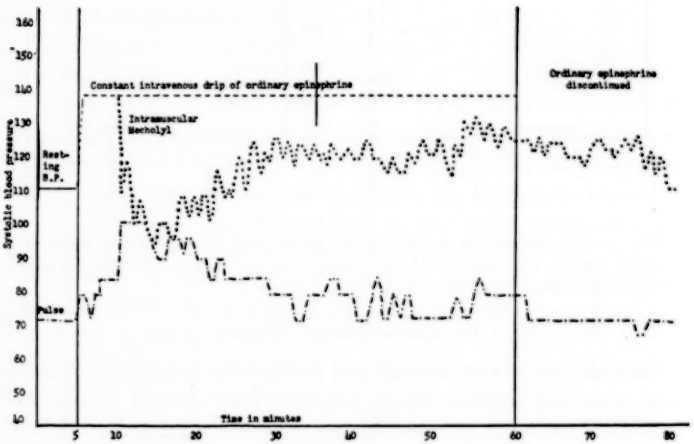

FIG. 3.—The effect of mecholyl on a blood pressure elevated by a constant intravenous infusion of epinephrine.

ranging from 21 years to 25 years. Each subject came in seven times, had his pulse and blood pressure taken, and received intravenous saline. All of the subjects became trained so that they could come in, lie down, and quickly establish their usual blood pressure and pulse level. After this had been accomplished, they were given a constant intravenous drip of epinephrine, and the flow was regulated until they had a constant level of systolic blood pressure 25 per cent above their basal level. When this was established, with the constant intraveneous

drip continuing, 10 mg. of mecholyl was given intramuscularly (the same dosage given the patients and the students during stress). Figure 3 shows the effect of mecholyl on such a chemically elevated blood pressure. On the succeeding day the same procedure was carried out, with nor-epinephrine being used instead of epinephrine (Fig. 4).

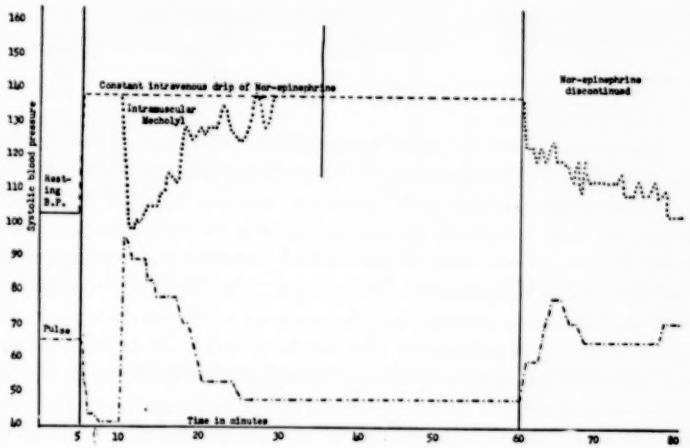

FIG. 4.—The effect of mecholyl on a blood pressure elevated by a constant intravenous infusion of nor-epinephrine.

The data obtained following the injection of mecholyl in these chemically elevated blood pressures were then treated in the same manner as the data obtained following the injections of mecholyl in psychiatric patients with elevated blood pressures and students who had elevated blood pressures during a stressful situation.

In all of the subjects whose blood pressure was elevated by epinephrine, following the injection of mecholyl the "Time of Homeostasis" was always greater than 25 minutes. (In fact, the cases were followed for 50 minutes without the preinjection level of blood pressure being reached in any of them.) When the blood pressures were elevated by a constant intravenous infusion of nor-epinephrine, an entirely different reaction took place and the preinjection level of blood pressure ("Time of Homeostasis" was reached in all cases during the observation period. The mean was 8.5 minutes, with a range of from seven minutes to 10 minutes.

The variables were then handled in the same manner as the same variables were in the patients and the students. "T" tests for significance of difference between the means were then done for "time,"

"area," and "fall," and these were found to be significantly different (Table III).

TABLE III.

	Time	*Fall*	*Area*
Epinephrine $\bar{X}$	> 25	39.9	72.0
Nor-Epinephrine $\bar{X}$	8.3	22.4	16.7
t = ...	55.667	5.670	17.020
p = ...	<.01	<.01	<.01

Comment. When the same measurements were applied and statistically analyzed—measurements of the mecholyl blood pressure reaction in normatensives whose blood pressure was first elevated by epinephrine or nor-epinephrine—it was found that the two groups corresponded with patients with elevated blood pressures and students who had elevated blood pressures during stress. The Group A reaction in both the psychiatric patients and the students under psychologic stress corresponded to that obtained with mecholyl when the blood pressure was elevated by a constant intravenous infusion of epinephrine in the experimental subjects; the Group B reaction in both psychiatric patients and the students under psychologic stress corresponded to that obtained with mecholyl when the blood pressure was first raised by a constant intravenous infusion of nor-epinephrine in the experimental subjects.

Discussion

The elevation of blood pressure under stress has been known for a long time. The two mechanisms shown by Hickam, Cargill, and Golden (22) were entirely similar to those which can be produced by epinephrine and nor-epinephrine in healthy normatensives as shown by Goldenberg, Pines, Baldwin, Greene, and Rog (18). In this study we found two types of elevated blood pressure in psychiatric patients and in students during psychologic stress: one type in which following the injection of mecholyl there was a failure of the blood pressure to reach the preinjection level throughout a 25 minute observation period; and another type in which the preinjection level was reached within the 25 minute observation period. A statistical analysis showed these to be different in regard to three variables (Tables II and III).

These same two types of elevated blood pressures can be produced in healthy normatensives, not under psychologic stress, by studying the effects of intramuscular mecholyl when they were given constant intravenous drips of epinephrine or nor-epinephrine on separate days and the results compared.

It can thus be seen that one type of elevated blood pressure induced by emotional upsets accompanying psychiatric illness, psychologic stress in students, and by the intravenous infusion of epinephrine in healthy normatensives not under psychologic stress, gave a similar pattern of blood pressure response after mecholyl (Fig. 5). In contrast

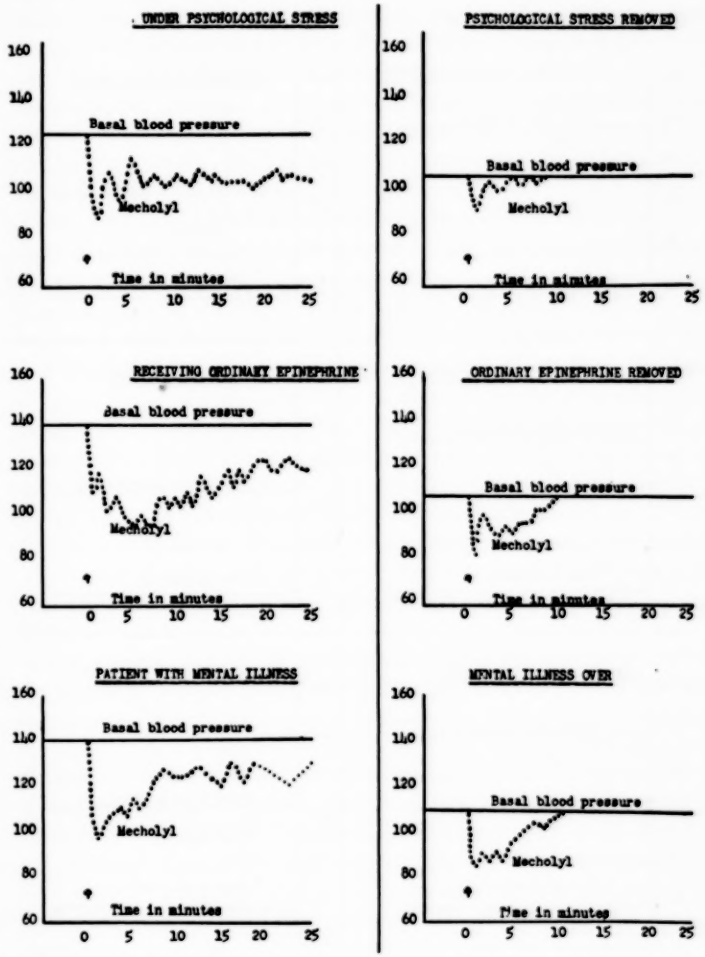

FIG. 5.—Similar patterns of blood pressure reactions after mecholyl in psychiatric patients with elevated blood pressures, in students with elevated blood pressures during psychologic stress, and in normatensives whose blood pressure was first elevated by an infusion of epinephrine.

to this, another type of elevated blood pressure induced by emotional upsets accompanying psychiatric illness, psychologic stress in students, and by the intravenous infusion of nor-epinephrine in healthy normatensives not under psychologic stress, gave a similar pattern of blood pressure response after mecholyl (Fig. 6). These two patterns also differed significantly in each of the three types of subjects in relation to the same three variables.

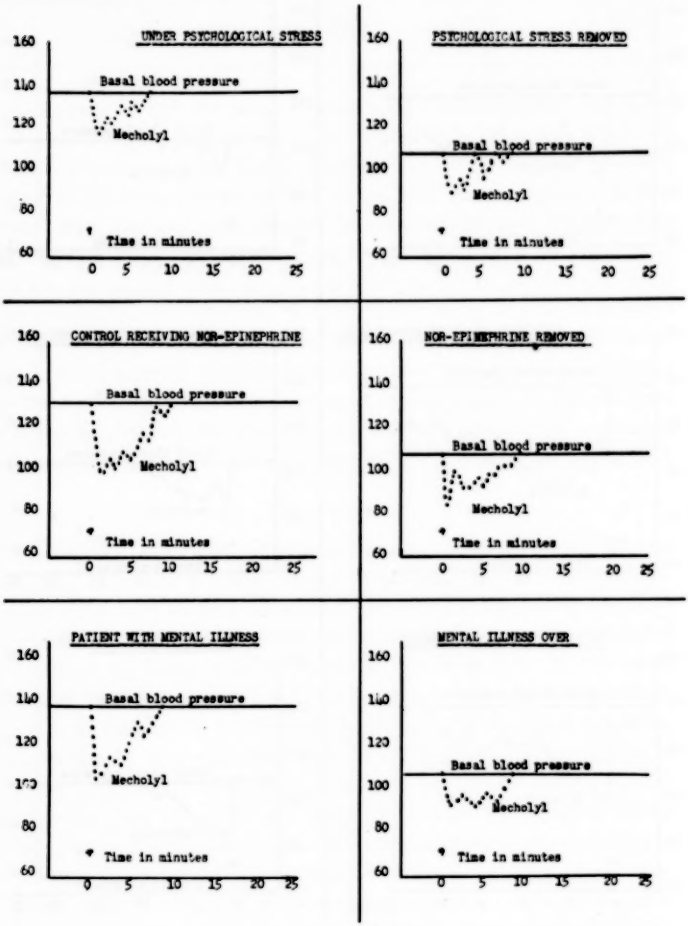

FIG. 6.—Similar patterns of blood pressure reactions after mecholyl in psychiatric patients with elevated blood pressures, in students with elevated blood pressures during psychologic stress, and in normatensives whose blood pressure was first elevated by an infusion of nor-epinephrine.

These experimental data argue strongly for the mediating substance in these two types of elevated blood pressure seen in psychiatric patients and in students under psychologic stress, being in one case an epinephrine-like substance and in the other a nor-epinephrine-like substance.

Evidence for the presence of epinephrine in the body is extensive (5, 19, 28, 33). Evidence for the presence of nor-epinephrine in the body is that v. Euler (7, 9) found by chemical analysis large amounts in the postganglionic sympathetic fibers in cattle. Stehle and Ellsworth (31), Greer, Pinkston, Baxter, and Brannon (20), v. Euler (7), and Gaddum and Goodwin (16) have shown that the effects of stimulation of the hepatic sympathetic nerves and the giving of nor-epinephrine were similar. Holton (23) has demonstrated by chemical tests nor-epinephrine in three pheochromacytomata. Goldenberg, Faber, Alston, and Chargaff (17) demonstrated by chemical means the presence of nor-epinephrine in the standard U.S.P. preparations of epinephrine derived from the adrenal medullae of cattle, and in removed pheochromacytomata. Page, Taylor, and Prince (26) offered convincing proof of the secretion by the body of nor-epinephrine.

Blaschko (4) suggested that nor-epinephrine was the precursor of epinephrine, the difference in the formula of the two substances being that nor-epinephrine lacks a methly group. He suggested, as have others, a theory that nor-epinephrine was associated with transmission down the postganglionic sympathetic fibers and that a methyl group was added at the point where adrenergic substances act. Transmethyliozation occurs frequently in the body, cholin and methonine which give up methyl radicals coming readily to mind. MacKenzie et al. (24) showed by using tracers that methionine donates methyl radicals in the adrenal medulla.

Bergen and Dale (3) in 1910 postulated that the sympathetic effector substance was not epinephrine but a catechol with a primary amine side chain. Tainter, Tullar, and Luduena (32) succeeded in making the optically active form of nor-epinephrine in 1947. A question much discussed today is whether or not this substance is the Sympathin E of Cannon (5). Among those who think that it is, may be mentioned, Bacq (2), Crismon and Tainter (6), and Greer et al. (20). Marazzi and Marazzi (25) think that nor-epinephrine is not Sympathin E. V. Euler (8) suggested the names Sympathin A and Sympathin N for epinephrine and nor-epinephrine, respectively. Any additional sympathetic transmitters discovered could then be designated by a different letter.

All the foregoing work cited is conclusive proof that the adrenal medulla secretes at least two substances, epinephrine and nor-epine-

phrine. The finding of two *distinct* patterns by us and by Hickam, Cargill, and Golden (22) raised the interesting problem of accounting for the purity of the reactions obtained. The following possibilities are suggested: the person secretes either one or the other substance; a mixture is secreted which depends for physiologic effects on which substance is secreted in greatest quantity at a given time; or there is dominance of one substance over the other no matter what the proportions of the substances.

None of our experiments precludes that there may be other chemical mediating substances which raise blood pressure. As stated at the beginning of this paper, we have eliminated from this report cases with elevated blood pressures in whom anxiety attacks were precipitated by either epinephrine or mecholyl, and the cases with cardiac, renal, or cerebral complications. The great degree with which the autonomic and psychologic responses of the patients eliminated from this study differ from those reported on is evidence that there are other chemical transmitters which raise blood pressure. We have made no effort to elucidate the role of the kidney (27), the posterior pituitary (21), or the adrenal cortex (30) in the present study.

It should be noted that we have used the terms "epinephrine-*like*" and "nor-epinephrine-*like*" in describing the substances which are the probable chemical mediators of the two types of raised blood pressure. Our findings are compatible with the theory that the two substances are, in fact, nor-epinephrine and epinephrine. However, the methods which we used of necessity involve some reasoning by analogy, and this makes us feel that this final step is not proved, and that it is best to apply the terms "epinephrine-*like*" and "nor-epinephrine-*like*" to the substances. In discussing the problems of experimentation in this field, Cannon and Rosenblueth (5) said that no one has seen the process whereby nerve impulses first produce a chemical substance and the chemical substance then provokes its peculiar effect in the reacting cell: the phenomenon is inferred. An excellent discussion of this entire problem can be found in Cannon and Rosenblueth's book (5). The experimental methods we used in these experiments were similar to those used in animals in studying the problem. Our findings are not complete proof that in these two types of elevated blood pressure, an epinephrine-like substance in one instance, and a nor-epinephrine-like substance in the other instance were the mediating chemical agents, but our findings are compatible with the theory that this is so.

Summary and Conclusions

1. One hundred psychiatric patients with elevated systolic blood pressures and 25 normatensive students who responded to a psychologic

stress-inducing situation with elevated systolic blood pressures were given standardized doses of mecholyl chloride intramuscularly and the systolic blood pressure followed for a stated observation period. The responses in terms of systolic blood pressure were divisible into two groups: (1) Group A, in which the drop in blood pressure following mecholyl was sustained and the preinjection level of blood pressure was not reached within the 25-minute observation period; (2) Group B, in which the drop in blood pressure following mecholyl was not sustained and the preinjection level was reached within the 25-minute observation period. Comparison of these two groups on the basis of three described variables showed a high probability that the groups represented distinct populations. Also, on the basis of two variables, obtained following the injection of mecholyl and described in the paper, Group A showed a significantly larger "Fall" and "Area" than Group B.

2. On the basis of the hypothesis that one type of elevated blood pressure was associated with excessive secretion of epinephrine, and the other with excessive secretion of nor-epinephrine, and that these could be differentiated on the basis of the blood pressure reaction following mecholyl, the following experiments were carried out:

Healthy normatensives, not under psychologic stress, were given on one day a constant intravenous infusion of epinephrine, and on another day a constant intravenous infusion of nor-epinephrine at a rate sufficient to stabilize their systolic blood pressures 25 per cent above their basal level. The same dosage of mecholyl chloride which had been given to the other subjects was then given intramuscularly while the blood pressures were being elevated by the intravenous infusions of the chemical agents. It was found that when the blood pressures were being elevated by the intravenous infusion of epinephrine, following mecholyl the falls in systolic blood pressure were sustained and the preinjection levels were not reached within the observation periods. In contrast to this, on other days, when the same subjects' systolic blood pressures were elevated 25 per cent above their basal level by means of a constant intravenous infusion of nor-epinephrine, the falls in blood pressure following mecholyl were not sustained and the preinjection levels were reached within the observation periods.

The data obtained from these two blood pressure patterns, produced by mecholyl when the chemical agent of the elevated blood pressure was known, were then treated statistically in the same manner as the data in the psychiatric patients with elevated blood pressures and the students who had elevated blood pressures during a psychologic stressful situation.

The elevated blood pressures due to infusions of epinephrine were

found to differ from the elevated blood pressures due to infusions of nor-epinephrine on the basis of the same three variables that Group A differed from Group B in the psychiatric patients and the students. The Group A reaction corresponded to the blood pressure elevations with epinephrine in regard to three variables, and the Group B reactions to the blood pressure elevations with nor-epinephrine in regard to three variables.

3. The experimental evidence offered suggested that the mediating substance in one type of elevated blood pressure in association with psychiatric illness and in normatensive students under psychological stress was an epinephrine-like substance, and in the other type of elevated blood pressure a nor-epinephrine-like substance. The blood pressure reaction following mecholyl seemed a reliable indicator of the type of elevated blood pressure which was present in a given case.

4. A discussion of the probale role of epinephrine and nor-epinephrine in sympathetic nervous system transmission was made.

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A STUDY OF THE EFFECTIVENESS OF DRUG THERAPY IN PARKINSONISM

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Criteria for the evaluation of the outcome in any treatment of parkinsonism are notoriously difficult to formulate. Previous studies which have attempted to evaluate the usefulness of one or another type of drug in abating the symptoms of the Parkinson patient have relied mainly on rather subjective standards. While a given mode of treatment may be clinically justified when sustained by the physician's subjective observation of the patient's apparent improvement and by the patient's testimony that he feels better and is able to get around better, nevertheless progress in methods of treatment and surely their rationalization would seem to require more objective bases for evaluating the outcome than have been hitherto utilized. A second limitation on most investigations in this area derives from the fact that experimental controls have rarely been carefully observed. Typically, insufficient allowance is made for individual differences among patients, effects of practice, and a variety of psychologic factors.

The present study is concerned with the evaluation of the comparative efficacy of artane, panparnit, and hyoscine in the treatment of parkinsonism. In our methodology we have used objective measures of improvement in addition to the usual subjective criteria. A careful experimental design has been enforced with as much rigor as an outpatient treatment service allows.

SUBJECTS

The subjects in the study include a total of 35 patients under treatment for parkinsonism in the Out-Patient Service of the Department of Neurology and Neurosurgery, Kings County Hospital. The group included 24 males and 11 females. The age range for men was 32 to 44 years. The age range for women was 35 to 63 years. Of the 35 patients 6 gave a history of encephalitis. In 2 cases arteriosclerotic etiology was

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established. In 27 cases the etiology could not be established with any reasonable certainty. Not every patient was involved in every inter-drug comparison for the reason that patients would from time to time miss appointments on testing days. Thus, the number of individuals involved in various inter-drug comparisons varies from 15 to 21, but it should be emphasized that in every single comparison the test data of the identical individuals who had one drug were compared only with their own data after they had been treated with the second drug involved in the comparison.

Criteria of Improvement

The criteria used for the evaluation of the various treatments consisted of the patients' subjective reports, the neurologic findings, and certain more objective data obtained by means of the electromyograph, the Purdue Pegboard, and the dynamometer. The subjective account took into consideration the individual's reaction to the drug therapy as reported by the patient and by relatives where possible. The neurologic examination included an evaluation of the general appearance, ability to get about, speech, gait, tremor, rigidity, and reflexes. All neurologic examinations were carried out by the same examiner. The electromyographic studies were made on a Grass six channel model 3C electroencephalograph using silver disc skin electrodes placed 3 cm. apart over the main mass of the muscles to be examined. For comparison, a one minute segment of myographic record was taken of the extremity with the greatest clinical disturbance. The recording was taken with the extremity at rest. The change in amplitude of spike potentials was used as an indication of the change in tremor. It was felt that the amplitude of the muscle spike potentials bore definite relationships to the degree of excursion of the extremity in tremor but that no definite relationship could be established between frequency or amplitude of spike potential on the one hand and rigidity on the other. The Purdue Pegboard is a device which is intended to provide measures of manipulative dexterity and requires the subject, in various sequences and under controlled conditions, to place small pegs in holes spaced in vertical lines on a board. Figure 1 shows the layout of the test. The pegboard was equipped with pins, collars, and washers grouped in separate recesses at the far end of the board. Five separate pegboard tests providing six different measures were used. The tests used, in the order in which they were given, were: (1) placing pegs with the preferred hand; (2) placing pegs with the opposite hand; (3) placing pegs simultaneously with both hands; (4) assembling pegs, washers, and collars in a prescribed sequence involving the simultaneous use of both hands in an organized way;

FIG. 1

(5) the shift test, requiring the patient to shift from use of the right to the left hand alternately and from an upward to a downward direction on demand, in response to a bell signal. The first four of these Purdue Pegboard tests comprise the standardized version of the pegboard examination as used in industry. The test was given in the prescribed manner with the exception that the time limits were doubled to allow for the patient's handicap. The score on each of these tests was the total number of pegs properly placed in the board. The fifth of the pegboard subtests was devised specifically for the purpose of this study. The shift or fifth test provides two measures; one for the total length of time required to place a prescribed number of pegs, and the other, a record of the total number of shifts which have been successfully performed in response to the signals. As may be seen, all tests involve initiation of movement, relatively gross maneuvers for reaching to the far end of the board, and finer co-ordination and finger-thumb

motions for grasping objects. The assembly test includes, in addition, a rather more active and complex organization of motor adjustment in that a multiple sequence of operations needs to be remembered and pursued. The shift-test measures are intended to provide an index of the patient's capacity to shift his motor adjustment in response to a given peremptory stimulus. These measures are obviously not of the same category as performance in the course of life adaptations, such as shaving, working at a job, rolling over and getting out of bed, but they do provide an opportunity for laboratory control and for objective observation, while not remaining limited to measures of tension, rigidity, and tremor out of functional contexts. The dynamometer was used to obtain measures of strength of grip for each hand, thus providing an index of available muscular power.

Procedure

The 35 patients were divided at random into four groups, each of which retained its identity as a group during the course of the study. Every patient was given all the tests prior to the inception of any treatment. Weekly or bi-weekly clinic visits were required in order to insure maximum cooperation on the part of the patients and for the regulation of the drug therapy.

Each of three groups was started on a different drug, one on artane, one on panparnit, and one on hyoscine. The patients of the fourth group were given a placebo. All medicaments, including placebo, were prepared in identical capsules which were not distinguishable in appearance. Each medicament was given in increasing doses so that by the third week maximum doses within the patient's tolerance were taken. At the end of the fourth week, the battery of tests was repeated and the dosage reduced for one week. At the beginning of the fifth week, each group was placed under a different treatment so that, for example, the group that initially had the placebo was given artane, the group that had artane was given panparnit, the group that had panparnit was given hyoscine, and the group that had hyoscine was given placebo. Again after a four week period of build-up on the given treatment, each member of the group was retested and, after one week of reduction of the drug, was reassigned to another medicament. In this way, at the conclusion of the 20-week period each individual had been exposed to all drugs and all drugs had had the advantage of occupying each position in the series as frequently as every other drug. It follows from this consideration that, since each subject served as his own control, individual differences in responsiveness were eliminated as were any effects accruing to practice. Furthermore, by the use of the placebo any ten-

dency to respond because of the psychologic factors involved in treatment rather than the specific pharmacologic properties of the drug could also be evaluated.

Results

Neurologic Examination.—In Table I the results obtained by subjective questioning and neurologic examinations are recorded. Because it was felt that so much of the clinical neurologic examination has a primary subjective element, evaluation of change was believed to be best reported as an over-all picture. While it was thought that variations in the state of rigidity and severity of tremor could be seen from week to week in some patients, by far the most prominent features seemed to be the outward appearance of the patient's ability to get about, speech, stance, and gait.

TABLE I

		Subjective Report			Neurologic Exam		
	No. Pts.	*Improved* %	*Worse* %	*No change* %	*Improved* %	*Worse* %	*No change* %
Placebo	33	18.1	63.6	18.1	6	42.4	51.5
Panparnit	35	62.8	20	17.1	31.4	8.5	60
Artane	32	65.6	15.6	18.7	40.6	6.2	53.1
Hyoscine	30	40	30	30	13.3	23.3	63.3

It may be noted that all of the drugs were superior to the placebo so far as the patients' subjective reports were concerned. Of 33 patients treated with placebo 18 per cent claimed general improvement, while 63.6 per cent complained of being worse. This contrasts with the fact that better than 60 per cent of the patients claimed improvement under panparnit and under artane. Hyoscine falls between placebo and the other two drugs. The physical findings on neurologic examination indicated far less efficacy for any of the treatments although the relative position of the drugs was roughly maintained. Again artane and panparnit were superior to hyoscine and all the drugs superior to placebo. Especially noteworthy is the fact that one was unable to pick up any evidence of significant neurologic change in from 51 per cent to 63 per cent of the cases. In this latter respect the drugs were hardly superior to placebo.

Electromyography.—As stated earlier, our electromyographic studies were concerned mainly with variation in amplitude of the muscle spike potentials which may be taken as objective measures of tremor. Table II shows the changes in amplitude under the four treatment conditions.

TABLE II.—Electromyographic Amplitude Changes Under Various Drug Conditions. N = 20

	Placebo	*Panparnit*	*Artane*	*Hyoscine*
Mean*	23.50	4.25	9.75	2.00
S. D.	25.91	23.95	27.59	28.21
S. D. M.	5.94	5.49	6.33	6.47
t	3.96	.77	1.54	.31
p	<.01	>.05	>.05	>.05

*Mean amplitude increase change represents increase in amplitude of tremor.

It will be noted that under placebo there was an average amplitude change of 23.5 microvolts and that this indicated a correlative increase in amplitude of tremor which is significant at the 1 per cent level of confidence. There were slight increases in spike potential under each of the three drugs but these were not statistically significant. Table III compares the amplitude changes under the three drugs with the changes occurring under placebo.

TABLE III.—Electromyographic Changes: Drugs Compared with Placebo. N = 20

	Panparnit-Placebo	*Artane-Placebo*	*Hyoscine-Placebo*
Mean Diff.	−19.25	−13.75	−21.50
S. D. Diff.	6.07	4.19	6.83
t.	3.17	3.28	3.15
p.	<.01	<.01	<.01

While the drugs themselves do not improve the level of tremor, each of them is clearly superior to placebo. In each case the mean difference in amplitude change is statistically significant beyond the 1 per cent level of confidence. It is important to note, however, that the superiority of the drugs over placebo does not represent a positive improvement. It is not that the drugs decreased the amplitude of the tremor, it is rather that under placebo the tremor becomes more marked. In this connection it must be noted that in three-quarters of the cases placebo was administered after the patients had become adjusted to one or another of the drugs. The implication seems to be that even though the drugs failed significantly to lessen the tremors, once a patient became accustomed to a drug its removal, even without his knowledge, resulted in an increase of tremor beyond the original base level.

Dynamometer and Pegboard.—The results with the dynamometer and the pegboard are presented together in three tables comparing performance gains under each of the three drugs with the gains under placebo. Table IV compares panparnit with placebo. Column 1 lists the

TABLE IV.—Performance Gains: Panparnit Compared with Placebo. N = 19

(1)	(2)	(3) Panparnit			(4) Placebo			(5) Panparnit-Placebo		
	Initial Performance	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Function	Mean	Mean	Mean Gain	t	Mean	Mean Gain	t	Mean Diff.	S. D.	t
Dynamometer right hand	27.55	27.11	−.44	.30	25.61	−1.94	1.21	1.50	1.71	.88
Dynamometer left hand	23.61	23.11	−.50	.48	21.33	−2.28	.93	1.78	2.05	.87
Pegboard preferred hand	19.63	22.74	3.11	4.71**	21.42	1.79	2.44*	1.32	.65	2.05*
Pegboard opposite hand	19.00	21.32	2.32	5.16**	21.37	2.37	4.84**	−.05	.59	.08
Pegboard both hands	13.31	14.89	1.58	3.29**	14.36	1.05	1.88*	.53	.62	.85
Pegboard organization	8.68	9.68	1.00	2.08*	9.94	1.26	2.80**	−.26	.40	.65
Pegboard shift-time	52.78	49.89	2.89	1.25	51.39	1.39	.48	1.50	3.69	.41
Pegboard shift-score	5.67	5.83	.17	.46	6.00	.33	1.46	−.16	.23	.70

*gain or difference significant at .05 level of confidence
**gain or difference significant at .01 level of confidence

various criterion functions. Column 2 presents the pre-drug performance means for the 19 patients who had been examined both after a course of panparnit and after a course of placebo.*

The mean right-hand grip was 27.55 kilograms, while the mean left-hand grip was 23.61 kilograms. By way of orientation it may be noted that the respective means for 16-year-old boys are 39.37 and 36.39 kilograms, while the means for 16-year-old girls are 28.70 and 26.56 kilos. The Purdue Pegboard figures are slightly above the means obtained by normals in half the time. Column 3a presents the mean performance in each function at the conclusion of treatment with panparnit, while Column 4a presents the data obtained at the conclusion of treatment with placebo. Columns 3b and 4b present the average gain in each function at the conclusion of treatment respectively with panparnit and with placebo. The ratios of these gains to their respective standard errors are given in Columns 3c and 4c. It will be noted that some of these t-ratios are marked with a single asterisk, others with a double asterisk. A single asterisk indicates that the t-ratio is of such magnitude that the actually obtained gain in performance would occur by chance not more than five times in 100 replications of the experiment if the true difference between pre- and post-treatment performance were zero. A double asterisk indicates that the obtained gain in performance level meets the 1 per cent level of confidence. Panparnit produced statistically significant gains in four of the Purdue Pegboard measures. But, then, so did placebo and, interestingly enough, in the identical functions. The differences between panparnit gains and placebo gains are given in Column 5a. These residual measures of improvement, after allowance for placebo effect, represent the net gain presumably ascribable to the pharmacologic influence of the drug. Panparnit proved to be superior in five of the functions, while placebo was superior in three. The standard errors of the mean differential gains are given in Column 5b. When the mean differential gains are compared with their standard errors, only one turns out to be statistically significant. Reference to the t-ratios in Column 5c shows that the net gain under panparnit in peg-placing with the preferred hand is significant at the 5 per cent level of confidence.

Table V compares performance gains under artane with those under placebo. Here, again, both the drug and the placebo produce their share of significant performance gains as a result of psychologic factors,

* These baseline figures are not identical with those given in Tables V and VI, comparing placebo with artane and hyoscine, respectively, because circumstances beyond our control prevented getting tests on all patients after each of the treatment periods. It should be recalled, however, that in every single comparison the identical individuals who had a given drug were compared only with themselves after they had been treated with placebo.

TABLE V.—PERFORMANCE GAINS: ARTANE COMPARED WITH PLACEBO. N = 21

(1)	(2)	(3) Artane			(4) Placebo			(5) Artane-Placebo		
	Initial Performance	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Function	Mean	Mean	Mean Gain	t	Mean	Mean Gain	t	Mean Diff.	S. D.	t
Dynamometer right hand	27.05	25.00	−2.05	1.83*	24.05	−3.00	1.99*	.95	1.38	.69
Dynamometer left hand	23.75	21.50	−2.25	1.50	20.90	−2.85	1.27	.60	2.51	.24
Pegboard preferred hand	19.81	21.62	1.81	2.70**	20.62	.82	1.06	.99	.64	1.55
Pegboard opposite hand	19.10	21.10	2.00	3.45**	21.33	2.24	3.45**	−.24	.60	.40
Pegboard both hands	13.14	14.91	1.76	4.76**	14.24	1.10	1.91*	.66	.53	1.26
Pegboard organization	8.81	10.05	1.24	2.95**	9.95	1.14	2.43*	.10	.38	.26
Pegboard shift-time	50.95	50.25	.70	.40	52.55	−1.60	.33	2.30	4.04	.57
Pegboard shift-score	5.70	5.90	.20	.91	6.00	.30	1.43	−.10	.07	1.43

*gain or difference significant at .05 level of confidence
**gain or difference significant at .01 level of confidence

practice, or both. Although artane produced superior results in six out of the eight functions, not a single one of the net gains, after allowance for placebo effect, was statistically significant. Individual differences in relative gains under artane and under placebo were so great as to overshadow any systematic tendency for artane to produce the better results.

Table VI compares hyoscine with placebo. Hyoscine is superior in seven of the eight performance net gains, but of these, only one, peg-placing with both hands simultaneously, appears to be statistically significant.

The three tables comparing drug gains with placebo gains list a total of 24 measures of net gain. In 18 of these, drugs turn out to be superior to placebo, while placebo is superior in six. However, of the 18 instances of drug superiority, only two involved net gains of sufficient magnitude relative to their standard errors to be statistically significant.

In addition to comparing the effects of the drugs with those of the placebo, the effects of the drugs were compared with each other for improvement in each of the eight functions measured. Only a single differential gain proved to be statistically significant. In peg-placing with the preferred hand there was a somewhat greater gain with panparnit than with hyoscine.

It seems a fair conclusion from the data thus far summarized that the three drugs, scarcely distinguishable among themselves for effect on pegboard performance, do seem to be slightly more effective on the whole than placebo. This inference is recommended less by any impact of clearly statistically significant net gains, and more by the somewhat consistent trend of the results. The greater part of the gains recorded appeared to be the result of practice, of psychologic effects, or of both. Furthermore, it must be emphasized again that in virtually each instance, the range of individual differences is so great as largely to overshadow the average relative gains.

Because gains in psychomotor performance appeared to be so largely independent of the particular mode of treatment, we became interested in the extent to which improvement might be a function of the individual patient. If the susceptibility of the patient rather than any specific property of the treatment were responsible for his improvement, then any tendency to gain or lose in performance efficiency ought to be constant throughout all modes of treatment. To investigate this problem we correlated each of the performance gains under each mode of treatment with the gains under every other mode of treatment. The resulting 48 intercorrelations as given in Table VII range from a low of —.01 to a high of .95.

TABLE VI.—PERFORMANCE GAINS: HYOSCINE COMPARED WITH PLACEBO. N = 15

(1)	(2)	(3) Hyoscine			(4) Placebo			(5) Hyoscine-Placebo		
	Initial Performance	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Function	Mean	Mean	Mean Gain	t	Mean	Mean Gain	t	Mean Diff.	S. D.	t
Dynamometer right hand	24.13	22.00	−2.13	1.63	20.73	−3.40	1.73	1.27	1.44	.88
Dynamometer left hand	21.87	21.53	−.34	.24	19.60	−2.27	.77	1.93	2.68	.72
Pegboard preferred hand	18.67	21.20	2.53	2.58*	20.07	1.40	1.27	1.13	.77	1.47
Pegboard opposite hand	19.07	20.67	1.60	2.62**	20.07	1.00	1.39	.60	.38	1.58
Pegboard both hands	12.87	14.80	1.93	3.52**	13.47	.60	.91	1.33	.72	1.85*
Pegboard organization	8.33	9.33	1.00	2.13**	9.27	.94	1.42	.06	.54	.12
Pegboard shift-time	54.87	54.47	.40	.12	57.33	−2.46	.35	2.86	5.94	.48
Pegboard shift-score	5.47	5.73	.26	.92	5.93	.47	1.57	−.21	.21	1.00

*gain or difference significant at .05 level of confidence
**gain or difference significant at .01 level of confidence

TABLE VII.—PERFORMANCE-GAIN INTERCORRELATIONS DISTRIBUTED ACCORDING TO DRUG PAIRS

Task	*Placebo-Panparnit* r	*Placebo-Artane* r	*Placebo-Hyoscine* r	*Panparnit-Artane* r	*Panparnit-Hyoscine* r	*Artane-Hyoscine* r
Dynamometer right	.39	.48*	.68**	.58**	.69**	.76**
Dynamometer left	.57**	.14	.43	.39*	.49*	.73**
Pegboard preferred hand	.57**	.61**	.73**	.68**	.52*	.84**
Pegboard nonpreferred hand	.21	.57**	.85**	.64**	.54*	.79**
Pegboard both hands	.29	.43*	.31	.38	.53*	.65**
Pegboard organization	.63**	.64**	.63**	.60**	.72**	.84**
Pegboard shift-time	−.01	.61**	.54	.76**	.95**	.82**
Pegboard shift-score	.89**	.95**	.75**	.61**	.71**	.94**

*correlation significant at .05 level of confidence
**correlation significant at .01 level of confidence

Thirty-nine of the correlation coefficients are significant at the 5 per cent level of confidence or better. The mean intercorrelation is .654 and this coefficient is significant at far better than the 1 per cent level of confidence. These findings indicate that, to a considerable extent, a patient who responds with improved psychomotor function in reaction to any one of the drugs is likely to show similar improvement in response to placebo. Contrariwise, one who shows little or no improvement in response to placebo tends to show a similar failure to improve with treatment by any one of the drugs. The indications for the operation of an individually consistent susceptibility for gain in psychomotor efficiency in response to treatment, regardless of its nature, seems to overshadow by far any differences among the drugs themselves and between drugs and placebo with respect to their efficacy in inducing improvement in psychomotor function.

We can only speculate at this time as to the nature of this individual susceptibility to improvement. In part, it may be the result of an artifact. Those individuals who at pre-treatment testing were caught on a particularly bad day, so that they produced minimal performance, would be likely to improve on all subsequent tests. Similarly, those individuals who at pre-drug testing were caught on a particularly good day, so that they performed at a level better than their average, could scarcely do other than reduce or at least restrict their subsequent per-

formances. In both instances a contribution would be made toward constancy of post-treatment gain. A second source of such constancy might reside in individual difference in physiologic susceptibility to the pharmacologic action of the drugs. That this source of constancy must be quite limited is shown in the fact that drug gains in general are only uncertainly and minimally superior to performance gains with placebo. Furthermore, intercorrelations among gains involving drug-drug comparisons were contrasted with intercorrelations among gains involving drug-placebo comparisons. The average drug-drug intercorrelation was found to be .71, while the average drug-placebo intercorrelation was found to be .59. The difference between these two average intercorrelations is not statistically significant, but it may be noted again that the trend is once more in the direction of some drug efficacy; this time in eliciting somewhat greater individual constancy of response.

A final source of constancy in response to treatment may reside in certain definable psychologic characteristics of the subjects. It may be that attitudinal set, ability to profit from experience, or other factors in the personality organization of the patient determine in large measure what the outcome of treatment will be. Investigation of psychologic factors will be undertaken as a next step in the analysis of our material. All of our subjects were given Rorschach and Figure Drawing examinations prior to the inception of treatment and at the conclusion of treatment. We are in the process of analyzing this material to check on the hypothesis that there may be a characteristic personality structure which is susceptible to parkinsonism, or which parkinsonism tends to induce by virtue of its polarizing and leveling effect on the reaction tendencies of its victims. But besides this end, it is our aim, by means of these projective tests, to explore any contrasts in personality organization which may exist between those of our patients who showed a constant tendency to gain in psychomotor performance irrespective of the nature of the treatment with those whose constant tendency was to gain very little or not at all.

Summary

1. The comparative efficacy of artane, panparnit, hyoscine, and placebo was investigated in a controlled study of 35 patients suffering from parkinsonism. Criteria of improvement included objective myographic, dynamometric, and pegboard dexterity tests in addition to the usual neurologic examination.

2. Drugs were definitely superior to placebo in eliciting from the patient with Parkinson's disease subjective reports of improved sense of well-being. Similar results in a lesser degree were obtained when the criteria of the neurologic examination were applied.

3. The electromyographic recordings indicated that the drugs used were not able to reduce the amplitude of the tremor as compared with the pre-treatment level. Once a patient became accustomed to a drug, its removal, even without his knowledge, resulted in an increase of tremor beyond the original base level.

4. Most of the psychomotor performances, excepting the dynamometer and the Shift Test on the Purdue Pegboard, showed fairly constant, statistically reliable improvement after all treatments, including placebo, as compared with pre-treatment level. In this respect there is a statistically unreliable suggestion of minimal superiority of drugs over placebo. The drugs are not significantly distinguishable from each other. Improvement in voluntary motor function tends to be consistent for the individual irrespective of the nature of the treatment.

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PREPSYCHOTIC PERSONALITY TRAITS IN MANIC DEPRESSIVE DISEASE*

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AND
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Introduction

Classically, the prepsychotic personality in manic-depressive disease is regarded as cyclothymic. The occurrence of such a personality is stressed by many authors. For example, Strecker, Ebaugh, and Ewalt (8) state, "In our experience, at least 24 per cent of the patients have had some type of up and down or cyclothymic personality pattern." They describe two extremes, "most commonly in his prepsychotic make-up the manic-depressive is a so-called extrovert. . . . These predominantly extroverted individuals are usually sociable, energetic, bright and cheerful with a strong tendency to go into action or to carry out their ideas and urges. They are usually neither reflective nor thoughtful . . . and often ideas are expressed which show poor judgment. . . . At the other extreme they are blue, pessimistic, readily discouraged and worry a great deal, often being overconscientious and dreading the future."

This is fundamentally in agreement with the descriptions of Henderson and Gillespie (6) who state, "The manic-depressive disposition is one in which the affect swings from states of elation to states of depression in people who are generally recognized to have frank, open personalities. They are either bright, talkative, optimistic, aggressive people, who make light of the ordinary affairs of life, or else they take a gloomy outlook, bewail the past, make mountains out of mole-hills; or there is a combination of the above moods, rendering the person emotionally unstable and variable." Similarly, Campbell (3) recognizes two types of cycloid personalities, a depressive and a hypomanic type; the former is a "conscientious, worrying, anxious . . . quiet and unassuming" individual, the latter is a "friendly, outgoing, aggressive, optimistic individual with considerable personality drive."

Other authors are at variance with this description or place different emphasis on certain aspects of the prepsychotic personality. Alexander

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(1) describes manic-depressive personalities as warm, out-going, often practical individuals who prefer the concrete over the abstract and whose emotions rule their reason. According to English (4) they are perfectionistic, egocentric, logical, wise, talented, and afraid to hate except when actually experiencing a manic attack. They have difficulty in accepting a new point of view and in relating warmly to others. He finds frigidity to some degree in all of the females.

Fenichel (5) describes them as narcissistic and oral and refers to them as "love addicts" who are incapable of loving. Oltman and Friedman (7) believe that those who have depressions are often perfectionistic, conscientious, and meticulous, while those who have elations are frequently extrovertive.

Method

Since there are some differences in emphasis on certain personality factors in manic-depressive disease, we tried to ascertain whether these differences could be accounted for by the association of particular personality traits with the traditional clinical types. Accordingly, the records of 50 manic-depressive patients treated on the psychiatric service of the University of Minnesota Hospitals were selected at random for the period 1941-1951. The final summaries, histories, and personality descriptions were reviewed in detail to learn if there were any common prepsychotic personality traits listed for the group as a whole, and whether there were any personality differences among those having depressions only, elations only, and those having both depressions and elations.

On the basis of the histories and final diagnoses, the 50 cases were divided into three groups: (a) those having depressions only, 24 cases; (b) those having depressions and elations, 15 cases; (c) those having elations only, 11 cases.

All of the adjectives and phrases describing each patient were listed and an attempt was made to classify these. From an analysis of these descriptions and using Webster's International Dictionary as a guide, 20 categories of adjectives were set up. These were:

1. *Shy* (including timid, retiring, reserved, bashful, withdrawn, secluded, secretive, tendency to avoid people, introverted)
2. *Sociable* (including friendly, affable, companionable, statements indicating tendency to associate with others, extroverted)
3. *Conscientious* (including faithful, scrupulous)
4. *Meticulous* (including perfectionistic, excessively careful about small details)
5. *Sensitive*
6. *Thrifty* (including frugal, economical, "tight-fisted")

7. *Reliable* (including trustworthy, trusty, dependable, responsible)
8. *Ambitious* (including eager desire for preferment, honor, power or superiority)
9. *Religious* (including "high moral and ethical code," "regular church attendance")
10. *Active* (including energetic, "peppy," "hyperactive")
11. *Egocentric* (including selfish, vain, egotistical, "cocky," attitude of superiority, "little regard for others")
12. *Self-reliant* (including self-confident)
13. *Insecure* (including uncertain, indecisive)
14. *Unstable* (including impulsive, emotional lability, temper outbursts, instability)
15. *Promiscuous* (including infidelity)
16. *Rigid* (including stubborn, obstinate)
17. *Dependent*
18. *Good Judgment* (including "good manager," "good common sense," capable, competent)
19. *Thoughtful* (including kind, considerate, generous)
20. *Intelligent* (This represented the informants' appraisal and included such statements as, "learned easily," "good learning ability," "intelligent," "good student," "rapid learner")

It should be emphasized that these categories were not arbitrarily set up before reviewing the cases but grew out of a study of the descriptions in the hospital records. All but a few of the adjectives or descriptive phrases could be conveniently placed in the above groups. Some of the unclassified adjectives seemed to describe aspects of behavior which were already classified in one of the other categories; for example, "talkative" in one case who had several other adjectives falling in the category *Active*. Others occurred so infrequently that it did not seem profitable to set up additional categories. That is, they were mentioned only once or twice.

Description of the Cases

The data regarding age at onset, sex, and number of attacks were as follows:

Age at Onset. The range and mean for the total sample and each of the three groups are given in Table I.

Considering age of onset by decades for the total sample, 12 (24 per cent) began in the second decade; 12 (24 per cent) began during the third decade; 16 (32 per cent) began during the fourth decade; and the remaining 10 (20 per cent) began after age 40.

Our finding of the majority having an onset in the 20-40 year age

group is in keeping with the findings of most authorities (2). The finding of 24 per cent with onset before age 21 is higher than reported by most authors.

TABLE I

	Range	*Mean*	*Mean for Females*	*Mean for Males*
Total cases (50)	13–52	30.5	30.5	30.5
Depressions only (24)	14–52	34.1	31.7	39.7
Depressions and Elations (15)	13–48	27.2	29.0	16.6*
Elations only (11)	16–52	27.0	28.0	25.8

* Three cases only.

Sex. Females outnumbered males in the whole sample and in each of the three groups. The distributions are listed in Table II.

TABLE II

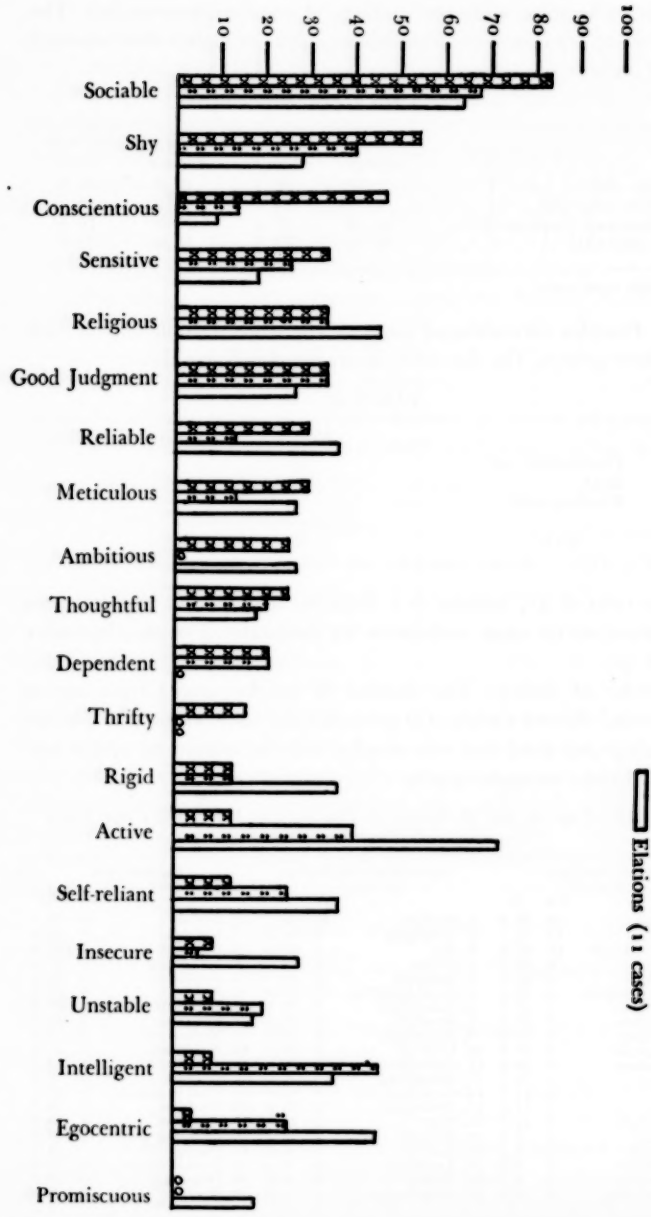
	Females	*Males*
Depressions only	17	7
Both	12	3
Elations only	6	5
TOTAL	35	15

This ratio of 2⅓ females to 1 male for total sample approximates ratios reported by most authorities for hospitalized manic depressive patients (2).

Number of Attacks. The number of attacks ranged from one to "numerous." Eleven patients (22 per cent) had only one attack. Twenty patients (40 per cent) had two attacks, and the remaining 19 (38 per-cent) had three or more attacks.

TABLE III.—List of the 20 Traits in Decreasing Frequency for Each Group

Depressions Only (24 cases)			*Depressions and Elations (15 cases)*			*Elations Only (11 cases)*		
	No.	*%*		*No.*	*%*		*No.*	*%*
1. Sociable	20	83.3	1. Sociable	10	66.7	1. Active	8	72.7
2. Shy	13	54.1	2. Intelligent	7	46.3	2. Sociable	7	63.6
3. Conscientious	11	45.8	3. Shy	6	40.0	3. Religious	5	45.4
4. Sensitive	8	33.3	4. Active	6	40.0	4. Egocentric	5	45.4
5. Religious	8	33.3	5. Religious	5	33.3	5. Intelligent	4	36.4
6. Good judgment	8	33.3	6. Good judgment	5	33.3	6. Rigid	4	36.4
7. Reliable	7	29.1	7. Self-reliant	4	26.6	7. Self-reliant	4	36.4
8. Meticulous	7	29.1	8. Sensitive	4	26.6	8. Reliable	4	36.4
9. Ambitious	6	25.0	9. Egocentric	4	26.6	9. Meticulous	3	27.3
10. Thoughtful	6	25.0	10. Unstable	3	20.0	10. Ambitious	3	27.3
11. Dependent	5	20.8	11. Dependent	3	20.0	11. Shy	3	27.3
12. Thrifty	4	16.7	12. Thoughtful	3	20.0	12. Insecure	3	27.3
13. Rigid	3	12.5	13. Conscientious	2	13.3	13. Good judgment	3	27.3
14. Active	3	12.5	14. Meticulous	2	13.3	14. Sensitive	2	18.1
15. Self-reliant	3	12.5	15. Rigid	2	13.3	15. Unstable	2	18.1
16. Insecure	2	8.3	16. Reliable	2	13.3	16. Promiscuous	2	18.1
17. Unstable	2	8.3	17. Insecure	1	6.6	17. Thoughtful	2	18.1
18. Intelligent	2	8.3	18. Ambitious	0	0.0	18. Conscientious	1	9.0
19. Egocentric	1	4.2	19. Thrifty	0	0.0	19. Dependent	0	0.0
20. Promiscuous	0	0.0	20. Promiscuous	0	0.0	20. Thrifty	0	0.0


10
20
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40
50
60
70
80
90
100
Sociable
Shy
Conscientious
Sensitive
Religious
Good Judgment
Reliable
Meticulous
Ambitious
Thoughtful
Dependent
Thrifty
Rigid
Active
Self-reliant
Insecure
Unstable
Intelligent
Egocentric
Promiscuous
Depressions Only (24 cases)
Both (15 cases)
Elations (11 cases)

Figure 1

Personality Findings

Our findings with regard to the twenty personality traits are summarized in Table III, and Figs. 1, and 2.

Table III lists these twenty personality traits in order of decreasing frequency for each of the three groups.

Figure 1 is a graphic representation of the percentage frequency of occurrence of these traits in each of the three groups, arranged in decreasing frequency for the depressive group.

Figure 2 is the same graphic representation, but arranged in order of decreasing frequency for the manic group.

Discussion

It is immediately apparent that there is a high frequency of sociable traits in all three groups. It should be emphasized, however, that our category of sociable, includes all degrees of sociability from marked extroversion to mere friendliness. This is important to bear in mind, particularly since many cases are also described as shy. Though this seems paradoxical, it is explained by the frequent occurrence of such descriptions as "quiet, but friendly," "a quiet, introverted person but able to relate to others socially," or "made friends easily though did not aggressively seek out friends." Shyness though common in all three groups is only one-half as frequent in the manic group as in the depressed group.

Another obvious finding is the high frequency of active traits in the manic group and their rare occurrence in the depressed group.

Another striking finding is the presence of egocentric traits in nearly one-half the manic group and their relative absence in the depressed group.

In regard to conscientiousness, this relationship is reversed, being found in almost one-half of the depressed group, but in less than 10 per cent of the manic patients.

Rigidity is mentioned three times more frequently (36.4 per cent) in manic patients than in depressed patients.

In general, the frequency of each trait in the mixed group lies somewhere between the frequencies of that trait for the manic group and the depressed group. The three most striking exceptions to this general relationship are found for the traits of ambitiousness (25 per cent of depressed, 27.7 per cent of manics, and 0 per cent of mixed); meticulousness (29.1 per cent of depressed, 27.3 per cent of manics, and 13.3 per cent of mixed); and reliable (29.1 per cent of depressed, 36.4 per cent of manics, and 13.3 per cent of mixed).

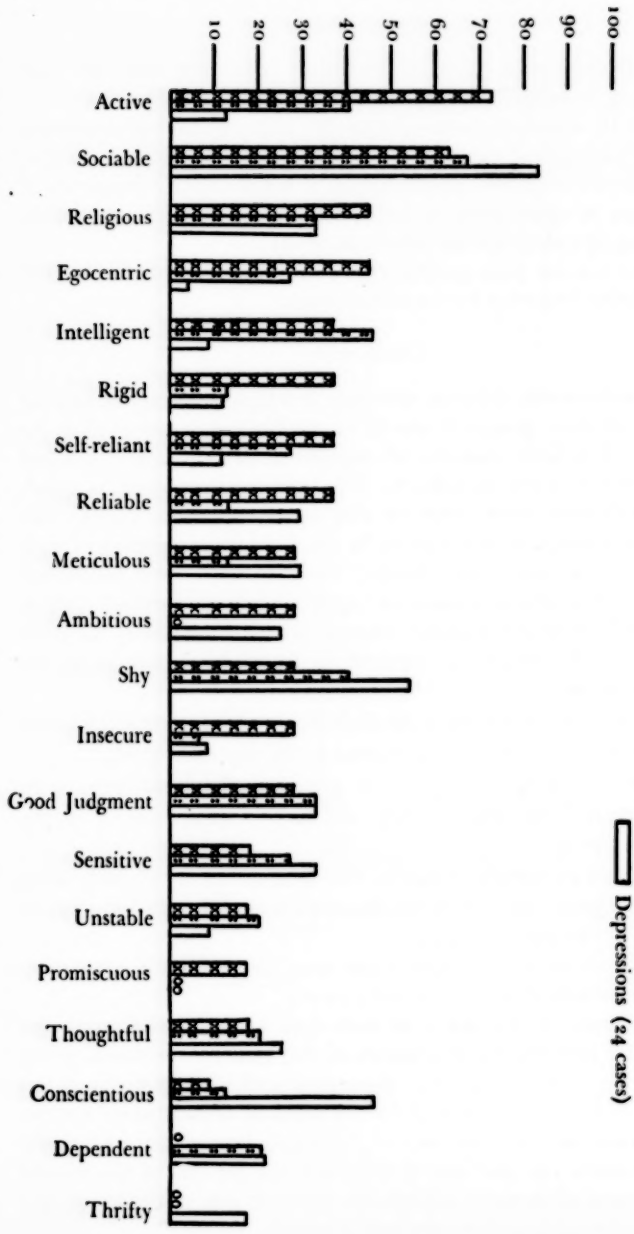
10
20
30
40
50
60
70
80
90
100
Active
Sociable
Religious
Egocentric
Intelligent
Rigid
Self-reliant
Reliable
Meticulous
Ambitious
Shy
Insecure
Good Judgment
Sensitive
Unstable
Promiscuous
Thoughtful
Conscientious
Dependent
Thrifty
Elations (11 cases)
Both (15 cases)
Depressions (24 cases)

Figure 2

A glance at Figs. 1 and 2 reveals that no good inverse relationship exists between the frequencies of individual personality traits for the manic and the depressed groups.

Conclusions

Using frequencies of approximately one-half and greater as "frequent," one-third to one-half as "common," and less than one-tenth as "rare" we arrive at the following descriptions of the three groups.

I. Depressions Only: These patients are frequently sociable to some degree, but often also shy and conscientious. They are commonly sensitive, religious, and possessed of good judgment. They are rarely described as insecure, unstable, "intelligent," egocentric, or promiscuous.

II. Both Depressions and Elations: These patients are frequently described as sociable and "intelligent." They are commonly described as shy, active, religious, and possessed of good judgment. They are rarely described as insecure, ambitious, thrifty, or promiscuous.

III. Elations Only: These patients are frequently described as active, sociable, egocentric, and religious. They are commonly described as "intelligent," rigid, self-reliant, and reliable. They are rarely described as conscientious, dependent, or thrifty.

Table IV summarizes the descriptions of the three groups.

TABLE IV

	Depressions Only	*Depressions and Elations*	*Elations Only*
Are	Sociable Shy Conscientious Sensitive Religious Possessed of good judgment	Sociable "Intelligent" Shy Active Religious Possessed of good judgment	Active Sociable Religious Egocentric "Intelligent" Rigid Self-reliant Reliable
Are not	Insecure Unstable "Intelligent" Egocentric Promiscuous	Insecure Ambitious Thrifty Promiscuous	Conscientious Dependent Thrifty

All three groups resemble each other in that they are frequently sociable, commonly religious, and possessed of good judgment. In addition, the manic group resembles the depressed group in that both are fairly often described as reliable, ambitious and meticulous.

The depressed group differs from the manic group in that the latter are frequently described as active and egocentric, are commonly considered "intelligent" but rarely described as conscientious. In contrast, the depressives are frequently conscientious, usually not active, and rarely considered "intelligent" or egocentric.

Summary

Fifty hospital records of patients with manic-depressive reactions were reviewed for prepsychotic personality traits. The records were divided into three groups depending upon whether the patients had depressed, mixed, or elated types of reactions. From the descriptions in these records, twenty categories of personality traits were established. The frequencies of these traits in each of the three groups were listed. A review of the data revealed that certain personality traits are commonly found in all three clinical types and that other personality traits are common to one type but rare in another.

1. All three groups are alike in that they are frequently sociable and often religious.

2. In addition, the manic and depressed groups are alike in that they are fairly often described as reliable, ambitious, and meticulous.

3. The depressives differ from the manics in that the latter are frequently described as active and egocentric, commonly considered "intelligent" but rarely described as conscientious. In contrast, the depressives are frequently conscientious, usually not active, and rarely considered "intelligent" or egocentric.

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INDUCTION OF SLEEP BY AUTONOMIC DRUGS*

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INTRODUCTION

The autonomic nervous system is involved in the physiologic mechanisms controlling levels of consciousness. This is suggested by the relationships between schizophrenia, epilepsy, sleep states, and autonomic function. Gellhorn (2) has recently reviewed data which point to the importance of the parasympathetic function in normal sleep. Hess (4) found that stimulation of the diencephalon anteriorly resulted in parasympathetic activity associated with a diminished responsivity of the somatic nervous system. At the same time sleep-like conditions were induced. Richter and Crossland (6) showed that in rats the acetylcholine levels were higher during sleep than in wakefulness and activity. It thus appears from both physiologic and biochemical data that normal sleep may be associated with relatively high parasympathetic activity compared to sympathetic activity.

In the development of the atropine test Hoffer (5) used the following combination of autonomic drugs, 1 mg. of atropine sulfate intramuscularly, followed 30 minutes later by 2 mg. of prostigmine sulfate intramuscularly, followed 15 minutes later by 200 mg. of acetylcholine bromide intravenously. Three female volunteers were used as subjects. Two of the volunteers stated that their eyes felt heavy and they felt sleepy during the injection of acetylcholine. Within a few minutes they both fell asleep and slept one hour. They were aroused and allowed to return home. Upon arriving home they were still sleepy. The third subject did not become sleepy but instead felt very alert. After arriving home she became very drowsy and at 8 P.M. (the experiment was started at 4 P.M.) became very sleepy. Her sleep was interrupted by vividly colored dreams, something rare for her.

Atropine sulfate blocks acetylcholine esterase. Prostigmine strongly inhibits this enzyme. Thus the net effect of the three drugs is to markedly increase parasympathetic tone but to prevent its muscarinic manifestations. The nicotinic action of the acetylcholine is undiminished (3), and the stimulant effect on the sympathetic ganglia is unaffected. It

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thus appeared that by inducing high parasympathetic nicotinic activity in normal individuals by means of drugs that per se have no hypnotic action in the quantities used, sleep was induced. The triad of drugs was, therefore, more thoroughly studied in a larger series of normal subjects, in epileptics and schizophrenics.

Method

The normal subjects had volunteered to participate in our schizophrenic research program using hallucinogenic drugs (1). Before volunteers were accepted, they were subjected to a battery of psychologic tests and the atropine test. These subjects were then given the triad of drugs but were told only that we were interested in the blood pressure response. Some of the subjects had continuous EEG records made during the entire test. The word sleep was not once mentioned to the subjects, in order to prevent suggestive induction of sleep. After the completion of the experiment the subjects were asked to record their impressions of the test the next day as a preparation for recording the results of their hallucinogenic interviews. The next day the purpose of the experiment was explained to them. All experiments started at 4:00 P.M.

Psychologic Results

A. *Normals.* The following subjective reports were received from the normal volunteers.

C.K.: "Received the test starting at 4:00 P.M. At 5:40—definitely feel drunk. I wobble when I walk and have difficulty in focusing my eyes and feel as if I had been on a good one. In driving home I was conscious of not being in top form. I noted the speed from time to time and kept below 20 m.p.h. At one point I felt that the car was going at about a 3 degree angle to the road although there was no sensation of sliding.

"My eyes bother me. I feel shaky and insecure physically. I feel on the verge of dizziness but not dizzy, about how I feel after several shots too many. I lurch a little and feel I should lurch more. Things taste awful. A cup of coffee was horribly bitter and unsatisfactory. I had to spit it out. A kid's program on the radio seemed so loud that I asked to have it turned down although it was okay to others. I went to bed at 9 P.M. and fell asleep immediately. I could recall fragments of two dreams neither of which was out of the ordinary or particularly vivid in any respect."

N.B.: "Doc finished soon after that and I sat up. I didn't feel there had been much to the test. I was a little dizzy when I sat up; it resembled the feeling I get after I read for quite a while. When I stood up I was really dizzy, almost drunk, because there was a kind of hazy feeling you get after

a couple of beers that makes you reel a little and closes in the size of the world you notice. I felt that if I went a little more than I had when I rocked my feet I would have gone over.

"Doc said he would drive me home and I followed him out. I was reeling a little around the corners of the corridor but I could navigate all right. We got into his car and came home. I was almost normal, felt a little tight inside and my sight was slow going from side to side. When I got home I started to hammer out this story. I was really dizzy then and a little sick but I could type fairly well and concentrate. I went down to supper and then I felt whoozy and like I could puke. The supper had no taste and I realized it was because the saliva glands were cut off. When I came upstairs I felt very tired and a little sick. I crawled into bed with my clothes on to sleep for about an hour. I was a while going to sleep in which I still felt dizzy and sick. I woke up at nine and was all right then but very tired. I took off my pants and went back to bed."

H.S.: "Received third needle which was almost immediately followed by a violent rushing sensation in my head. My hearing and speech seemed unaffected but my vision was definitely disturbed. This reaction so startled me that I failed to assess my immediate reactions properly. At the same time I had an almost overpowering desire to sit up. My vision was swimming and it was impossible to focus exactly. I had a definite sensation that I was seeing two images instead of one. These images appeared to cross over from left to right very rapidly. All objects appeared to be covered with a slight but highly illuminated haze. I experienced a heaviness of the head and (it) was accompanied by a heaviness of the eyes although I had no desire to close my eyes and attempt to sleep. The heavy, weary sensation was closely akin to that experienced when aircrews are subjected to a few times gravity during the time centrifugal force operates in the pull-out of a dive.

"I began to return to normal very rapidly and in a few minutes I felt okay although I was somewhat shaky, with my vision only slightly impaired. I returned home and became very drowsy after supper."

He then went to bed at 6:30 P.M. which for him is unusual as he normally retires around 1 to 2 A.M. Dropped off into sound sleep, awakened and slept again. Awakened at 9:00 and again fell asleep at 10:00 P.M. His fatigue was now gone, but he slept well. He had a nightmare in which he was looking at something with numbers on it. Slept until 8:00 A.M.

C.L.: Immediately after the injection of acetylcholine his eyes felt very heavy and the lids were forced to close. He felt sleepy "above" but wide awake "below." This lasted about two minutes and he felt as if he could go to sleep. He left the laboratory at 5:00 P.M., driving his own car. Vision was normal, he was normally alert and stated he felt real good, quite exhilarated. He drove home through congested downtown streets although he had previously agreed to drive along the edge of town. During the drive he felt very bold and was quite reckless at intersections. When he arrived home he felt dizzy and the room appeared dark. At 5:40 his mouth was

very dry and he felt tired. He had supper and found the taste of every mouthful of food markedly accentuated and highly flavored. The bread had some taste. At 6:30 he fell asleep on the couch where he slept until midnight, although he had planned on going to church with his father-in-law. At midnight he went to bed and slept until 6:30 A.M. He has taken sleeping pills but they have not induced sleep in him in the same way.

J.S.: "All of a sudden after the third needle images started coming which I definitely had not chosen to think about—images about people, close-ups of faces, some animals. These images came on at a nicely paced rhythm, never remaining long enough for me to really make any meaning out of them. Then I deliberately tried to concentrate on an image—part of my work—but could hold this image for only a fraction of a second—it would be overpowered and swept away by these other images. I let these images take over for another little spell. Then I tried deliberately to concentrate on a definite image—my boss—but again I could only hold the image for a fraction of a second, again being overpowered by those successive images. During this part of the test I could hear them talking. Also during the intravenous injection a feeling came over me that I wanted to laugh and I felt my mouth take the position of a definite wide grin. I actually fought against this since I could see no reason for wanting to laugh, and there were moments when I felt my mouth suddenly revert to a neutral position.

"Suddenly there was a pounding on the window connecting the room where I lay and the room containing the recording apparatus. I opened my eyes and saw the doctor. I felt rather groggy; my speech muscles didn't seem to work properly and caused indistinct pronunciation of the words. Also I felt wobbly as I walked. Upon arriving home I had supper but didn't particularly feel hungry. I was easily annoyed, as a matter of fact I reacted rather gruffly toward my wife when she mentioned someone had phoned me and I was to call back, but she did not know the number; she had forgotten it. Normally I don't react that way toward my wife. I seemed anxious to know who it was that was calling my wife. Normally I would simply take the attitude well—so the guy called and I wasn't home. I arrived home at 7:30. At 10:00 P.M. I felt very sleepy and my legs felt heavy on lifting them in walking. I went to bed. Had a very good sleep, did not dream at all."

W.B.: "On leaving the hospital the dryness in my mouth slowly began to return, but my vision remained blurred. On arriving home I felt quite exhausted, my stomach was slightly upset, and my blurred vision tended to make me tired. I arrived home at 6:30, took a bath at 7:00, lay down one half hour after the bath as I was tired. My head felt heavy. Arose about 7:30, had supper, and went to bed about 8:30. I usually go to bed about 11:30. I was very tired; have not been so tired recently. When asleep I had a bad dream and woke up. My wife later told me I got out of bed and said I was going to get some steel for my firm. I would awaken and then not remember why I had awakened. According to my wife I had a very restless sleep and I was very disturbed."

Comment: Common to all of the subjects was the feeling of tiredness and sleepiness that came on shortly after the injection of the acetylcholine. The subjects were all able to stay awake between a few minutes to several hours after the test but then sleep overpowered them and they all went to sleep many hours before their normal bedtime. In some the sleep was marked by restlessness and disturbing dreams and one subject had color dreams. Since none of the subjects suspected what this combination of drugs might do they cannot be said to have succumbed to suggestive factors inducing sleep. It is interesting that disturbances of mood, euphoria, lack of judgment, irritation, distortions of perception all occurred in some of the subjects.

It thus appears that increasing parasympathetic tone can induce sleep in normal subjects.

B. *Epileptics.* Three epileptics were similarly examined and closely observed before, during and after the experiment.

O.K.: Before the test at 2:00 P.M. he was normally alert and co-operative. When questioned immediately after the experiment, he denied having slept or feeling drowsy, and estimated his stay in the EEG laboratory to be about 45 minutes (EEG evidence showed marked sleep patterns and the total experiment required 110 minutes). He slept soundly for one hour after supper, was quiet and did not participate in ward activities. When he was wakened from his sleep he hallucinated a dollar on the floor under the table. He slept eight hours during the night and claimed he had not slept at all.

O.N.: Before the test he was quiet and co-operative. After the test he walked with a staggering gait and stated he felt "whoozy." He went to sleep one hour before his usual time and slept nine hours.

O.B.: Before the test she was quiet, reserved, and co-operative. After the test she was very drowsy and required assistance in walking back to her room. Ate a small supper and rested on her bed most of the evening afterward. She slept eight hours.

Comment: The EEG in all of these patients showed marked sleep activity. These results are reported by Szatmari (1954). It is interesting that, although there was clear-cut objective evidence of increased sleep activity and decreased ward activity, only one patient referred to his subjective experience.

C. *Schizophrenics.*

O.T.: Was alert and interested in ward activities before the test. After the experiment, he stated he had not been asleep nor sleepy during the test

but did feel sleepy after it was over. Complained of dizziness. That evening he joined in ward activities with some persuasion from nurses.

A.B.: Before the test she was talkative and elated, mixing well with other patients, relating amusing incidents of family life and joking with nurses. Immediately following the test she claimed that she had not slept but felt far away and had day dreams that were neither pleasant nor unpleasant. Patient was now reticent and required prompting to volunteer this information. Later complained she was dizzy and thirsty. Did not participate in activities as freely. This patient had just recovered from a schizophrenic attack as a result of ECT. The experiment reproduced her pre-treatment personality and behavior. By the next morning she was again completely well.

D.B.: Before the test he was quiet, pleasant, but did not participate in ward activities. Immediately after the test he denied feeling sleepy. Some time later he complained that he was dizzy. There was no change in his behavior.

P.K.: Participated well in ward activity before the test. Afterward complained of unsteadiness. Very quiet in evening, had nausea and headache. Slept nine hours. The EEG showed fully developed sleep activity.

K.B.: On return from EEG, the patient walked unsteadily. She was disturbed and cried, blaming herself for failing to co-operate. She felt far away. Later she developed a fear that she might die. Was quiet and not participating in ward activities as well as usual. Her schizophrenic behaviour was accentuated. No change was observed in her EEG pattern.

Comment: Sleep activity was induced in only 1 of the 5 schizophrenic patients tested. Rather interesting was the reversion of the schizophrenic patient A.B. to her pre-ECT personality and behavior and the induction of a dreamlike state shortly after the injection of acetylcholine. P.K. showed fully developed sleep activity on EEG but did not complain of being sleepy. K.B. showed no sleep activity but did become more markedly schizophrenic.

Discussion

The induction of high parasympathetic nicotinic activity by means of atropine, prostigmine, and acetylcholine appears to decrease the level of consciousness. EEG examination confirmed this (high amplitude slow waves, spindles and hump parietal. The question as to whether this is due to all three drugs when given in proper sequence or to atropine alone is not solved. It is likely that prostigmine must be given before the acetylcholine in order to prevent rapid destruction of acetylcholine. Atropine alone is a cerebral stimulant in the dosages used.

Many atropine tests, Hoffer (5) have been performed on normals, neurotics and psychotics and rarely does it induce sleep in the subjects.

The change in the level of consciousness in normals was manifested by an increase in fatigue, a desire to sleep, and a decrease in insight. In schizophrenics, the change pointed toward an intensification of the disease process. In epileptics, the most marked sleep activity occurred on EEG but there was little change in sleep behavior.

Conclusions

From subjective accounts of normals and objective evaluation of epileptics and schizophrenics it appears that when the parasympathetic nicotinic activity is raised pharmacologically to a high level it induces a decrease in level of consciousness in the form of sleep, and in aggravation of schizophrenic symptomatology.

Summary

Atropine, prostigmine, and acetylcholine when given in that order induce sleep states in normal subjects as determined from subjective accounts. In epileptics and schizophrenics there was objective evidence for decreased levels of awareness, more marked in the epileptics and the schizophrenic patient who had recovered after ECT.

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AN ACTIVE TREATMENT PROGRAM FOR CHRONICALLY ILL MENTAL PATIENTS

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The relegation of chronically ill mental patients to the so-called "back wards" of a hospital for purely custodial care has long been a problem of mental institutions. This has led to a rising census and a feeling of hopelessness and futility on the part of the patient and his family. Because of this difficulty it was decided to institute an active therapeutic program with patients in this situation in the hopes of effecting a change in their status, and to evaluate certain therapeutic measures at the same time. The purposes of our investigation were as follows: (a) to determine the value of an active treatment program among chronically ill mental patients; (b) to compare and evaluate ECT, histamine, and group therapy for use with these patients; (c) to attempt to correlate the relationship of gastric hypoacidity and inadequate liver function with the therapeutic results obtained.

Clinical Material

The work was carried on in the continued treatment service wards of the Rhode Island State Hospital for Mental Diseases, Howard, Rhode Island. A random choice of 92 patients was made from among those with diagnoses of schizophrenia, manic-depressive, and involutional psychoses. The diagnostic categories were made by routine hospital measures with the age distribution ranging from the age of 16 to 73. The mean age was 35 years. Most patients were in for their first hospital admission and had been placed on the continued treatment service because earlier treatment had been of no avail. Only 19 patients, or 20 per cent, of the series had had previous hospital admissions. The length of hospital stay before the onset of the treatment program ranged from eighteen years to one month, with a mean of two and one-half years. Only one patient in five, or 20 per cent, was receiving ECT for the first time.

Procedures

All patients received detailed physical and mental examinations. They were placed in a group to receive ECT or ECT with histamine base prior to the onset of the therapy, and were not isolated from the

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other ward patients except during the treatment periods, receiving no other forms of therapy except as discussed in the paper. All 92 patients received liver function studies consisting of icteric index and cephalin-flocculation tests prior to the onset of therapy. In the middle of the treatment series, the patients were again tested for adequacy of liver function, and one week following the completion of the therapy program, the patients received the two afore-mentioned tests, plus thymol turbidity studies (the latter test was not used throughout because of a lack of availability of necessary constituents for a period). Also, on 16 patients of the series, a gastric tube was passed just prior to ECT and one specimen was collected. Another was collected at the height of the convulsion, and a third two minutes following recovery. Blood pressure readings were made before, during, and after histamine therapy for the first three therapy sessions to record the response of the individual to the histamine substance. Epinephrine and intravenous fluids were kept close at hand at all times during the therapy sessions.

Therapy Program

ECT was administered to the patients on Monday, Wednesday, and Friday mornings. Electrodes were applied in the routine fashion to allow passage of the current through the frontal lobe areas, and a Reiter apparatus was used at all times. All schizophrenic patients were carried to 20 grand mal seizures as recommended by Kalinowsky (14). Other patients were carried to symptomatic improvement, plus two treatments. In some affective disorders, where the schizophrenic features were well evident and no improvement noted, the patient was frequently carried to 20 grand mal seizures.

Forty-two patients of the series received ECT alone, and 47 received a combination of ECT and histamine therapy. Three patients received histamine therapy alone because permission for ECT was not forthcoming from the family, and these 3 are included in the combined group. Histamine therapy was administered via the intramuscular route on Monday, Tuesday, Thursday, and Friday afternoons. All patients in the histamine therapy group were carried to a total of 20 treatments. Patients receiving histamine were placed in a room just off the ward, and were dressed in pajamas before being placed in bed. Three milligrams of histamine base (in a histamine diphosphate solution) in 7 cc. of normal saline was administered. The injections were made one-half hour apart in equally divided doses. If the patient illustrated none of the usual histamine responses, such as flushing, tachycardia, etc., an increase of dosage of 1 mg. was usually sufficient to produce the desired results. In 2 patients there were marked blood pressure falls, and the

dosage was decreased 1 mg. with no further difficulty. In a third patient the fall of pressure was so marked that it was necessary to discontinue histamine therapy for one month. She was then started on the course again, and was continued on the optimum dosage to the completion of the therapy without further difficulties. It was our desire to begin the histamine therapy simultaneously with the onset of the ECT, but in a few cases this was not feasible because of a delay in receiving permission from the families.

Group therapy sessions were conducted for all patients of the series. The groups consisted of 10 to 12 patients, and were held in a room on the wards. Patients were seen for one hour bi-weekly. One-third of the patients in the series began group sessions while awaiting the onset of the organo-therapies. No one school of group therapy was followed in these sessions.

Criteria

The results of the combined therapies were classified into improved, benefited, and unimproved categories. Improvement was considered related to the therapies only in those cases where changes were noted during therapy or within three weeks of the completion of therapy and were maintained. Improvement was broken down into two classifications: (a) where the alleviation of symptoms was sufficient to allow the patient to leave the hospital; (b) improvement sufficient to allow the patient ground permission on a convalescent status, although not sufficient to allow to return to the community.

"Benefited" indicated improvement in symptoms and behavior, but not to the degree to warrant ground privileges or a return to the community.

All patients showing no marked changes for the better were classified as unimproved.

Results

Of the 92 patients, 50, or 54 per cent, fell into the definite improvement class, indicating release from the hospital or ground privileges. The total benefited was 18 patients which yielded a total of 68 patients assisted by the treatment program. There were 24 patients showing no change for the better. Twenty-five patients, or 27 per cent, left the hospital and 25 patients achieved ground privilege convalescent status. Thirteen patients, or 52 per cent, were in the group that had been hospitalized six months or less prior to the onset of therapy. Five, or 20 per cent, of those leaving the hospital were in the seven to 12 month group (see Table I), 4 in the 13 to 18 month category, and the remaining patients were scattered throughout the other classifications.

TABLE I.—Distribution of Length of Hospital Stay Prior to Therapy

Duration	*No. of Patients*	*No. of Patients With Previous Hospitalization*	*Total No. Improved*	*No. Leaving Hospital*	*No. Convalescent Status*	*No. Benefited*	*No. Unimproved*
6 Months or less	24	8	22	13	6	3	2
7–12 Months	10	2	8	5	2	1	2
13–18 Months	14	3	11	4	5	2	3
19–24 Months	10	—	7	1	1	5	3
2–3 Years	11	4	7	1	3	3	4
3–5 Years	6	1	4	—	3	1	2
Over 5 Years	17	3	9	1	5	3	8
TOTALS	92	21	68	25	25	18	24

Of those patients achieving ground privilege status, 6 fell into the six months or less category, 5 into the 13 to 18 month group with a similar number, surprisingly enough, falling into the over five-year classification. The failures, it will be noted, increased as the length of hospitalization prior to the treatment program's onset increased.

The largest number of improvements was seen in the diagnostic category of paranoid schizophrenia, where 19, or 28 per cent, of the total improvements were noted. Thirteen of the unspecified and 9 of

TABLE II.—Distribution According to Diagnosis

Diagnosis	*No. of Patients*	*No. with Previous Previous Admission*	*Total No. Improved*	*No. Leaving Hospital*	*No. Convalescent Status*	*No. Benefited*	*No. Unimproved*
Schizophrenia							
Catatonia	15	1	9	2	1	6	6
Hebephrenia	4	1	1	—	—	1	3
Paranoid	21	2	19	6	8	5	2
Unspecified	22	5	13	4	8	1	9
Manic-Depressive							
Manic	10	4	10	5	2	3	—
Depressed	15	6	13	6	5	2	2
Involutional	5	0	3	2	1	—	2
TOTALS	92	19	68	25	25	18	24

the catatonic schizophrenics showed improvement. Only one hebephrenic of the series was benefited by the program. Thirteen manic-depressive depressed (6 of whom had previously been diagnosed senile psychosis), and 10 manic-depressive manics improved. Three of the involutional psychotics showed improvement (see Table II).

The comparison of results between the group having ECT and those receiving ECT combined with histamine base is seen in Table III,

TABLE III.—A Comparison of Results with ECT and ECT with Histamine

	ECT						*ECT & HISTAMINE*					
Diag.	*Total No. Pat.*	*Total No. Imp.*	*Left Hosp.*	*Convl. Status*	*Benefited*	*Unimp.*	*Total No. Pat.*	*Total No. Imp.*	*Left Hosp.*	*Convl. Status*	*Benefited*	*Unimp.*
Schiz.												
Cat.	2	2	1	—	1	—	13	7	2	1	4	6
Heb.	—	—	—	—	—	—	4	1	—	—	1	3
Par.	11	9	4	4	1	2	10	10	2	4	4	—
Unspec.	8	6	3	2	1	2	14	7	—	6	1	7
Manic Dep.												
M-D-M	9	9	5	1	3	—	1	1	—	1	—	—
M-D-D	9	8	5	3	—	1	6	5	1	2	2	1
Invol.	3	1	1	—	—	2	2	2	1	1	—	—
TOTALS	42	35	19	10	6	7	50	33	6	15	12	17

assembled with diagnostic categories. It is to be readily seen that the results with ECT also are somewhat better (83 per cent of the patients in the ECT group showing improvement), while with the combined therapy 66 per cent of the individuals showed improvement.

Laboratory Correlation

Although extensive laboratory studies were undertaken, the results were such as to prevent correlation or interpretation because of the bizarre pattern response. This part of our work is considered to be a failure. However, it is hoped that at some future date a more reasonable correlation may be achieved under more constant control measures, since it is believed by some that such a tie-up exists.

However, the gastric secretion response on a quantative analysis may be visualized in Fig. 1, and illustrates the marked response on hydrochloric acid outflow at the height of the convulsions with a gradual diminishing in the recovery phase. Our findings correlated well with those of Sachler and his group (18) and others who noted gastric hypoacidity. While some attribute the rise of gastric acidity to the release of a histamine-like substance, we feel that the response is due to the forced contracture of the stomach musculature during the convulsive phase; this might lead one to assume that the gastric hypoacidity seen in psychotics may be due to a secretory dysfunction rather than to other

causes, such as seen in pernicious anemia, etc. Since our series consisted of so few patients more definite conclusions cannot be drawn.

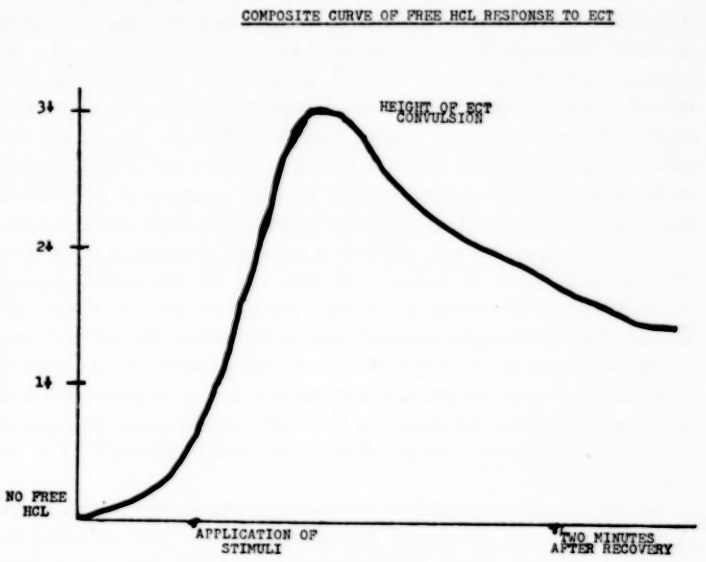

FIG. 1.

DISCUSSION

Our results produced interesting findings on a practical level. It is to be reiterated that in this paper we do not attempt to indicate "cures" or even recovery status. The desire was to effect change for the better in the hospitalization position of our patients, and to return to the community as many as possible. It is the conviction of this writer that if a chronically ill mental patient is returned to his family and the community for a period—though it may be only two to six months—that we have salvaged that much more for the individual. We feel that this was accomplished to some degree in our project. Twenty-five patients did leave the hospital, and 25 more achieved the convalescent status of ground privileges with a possibility of return to the community (or to closed ward service). Nevertheless, regardless of the short duration of the changes in status that may occur, all this gain is considered a plus factor.

In regard to the comparison of ECT with histamine, it is our feeling that with chronically ill mental patients histamine has no value over ECT. It is not our purpose to state definitely against histamine as a

therapeutic measure, but in our work histamine did not illustrate any particular value. ECT is still considered to be the better means of effecting change of status in hospitalized psychotics. Its ease of administration and its relative innocuousness still continue to make it a highly desirable—although empircal—method of therapy. The response of various diagnostic categories to ECT, as previously reported, was confirmed in this series with paranoid schizophrenic and manic-depressive depressed showing better results, and hebephrenics illustrating the poorest responses. While we were unable to employ psychologic testing methods to evaluate our observations, we were unaware of any clinical manifestation of brain damage to our patients as a result of the organotherapies. One patient, who expired of coronary thrombosis some time after the completion of therapy and who had not responded, showed areas of brain degeneration at autopsy, which were present, in the estimation of the pathologist, a considerable period before therapy had been instituted. It was observed that patients showing anxiety and a tendency to develop increased symptomatology toward the end of their series had better prognosis than did those that held their improvement throughout the series. This agrees with the observations of Kalinowsky (12) in his work.

Group therapy was used as a common denominator in this series. Although patients developed strong attachments and antagonisms in their immediate group, they attended most readily and with a show of enthusiasm. Throughout the sessions it became increasingly clear that they could easily recognize the bizarre thinking of others in their class but, nevertheless, could not accept the reality of their own illnesses. It was the major factor responsible for the slow pace encountered in these sessions.

While it is our feeling that group therapy has little value as a dynamic psychotherapeutic approach to chronically ill mental patients, we feel that it should be employed throughout hospitals with long-term patients. Its use should include all patients of the hospital regardless of the diagnostic categories involved, and need not be run by the physician, but by a nurse or attendant under his supervision. It affords the patient the feeling that someone is taking an interest in him and his problem, and that something is being done to help him. It also destroys in hospital personnel the attitude that mental hospitals are custodial institutions, and tends to break down the negative resistance toward new programs that one so readily encounters.

Summary

1. Ninety-two patients from the chronic wards of the Rhode Island State Hospital were used in an active treatment program.

2. Forty-two patients received ECT alone, and 47 received ECT combined with histamine, with 3 receiving histamine alone.

3. Group therapy was a common denominator of the series, and liver function adequacy was studied.

4. Comparison of results between ECT and ECT with histamine are discussed.

5. ECT is still the most reliable form of therapy in mental hospitals.

6. Liver function studies were inconclusive.

7. Group therapy should be employed extensively with hospitalized psychotics.

The author wishes to express his graittude to Jeremiah Sullivan, R.N., for his valuable assistance in this program.

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AN UNUSUAL FAMILIAL CEREBELLAR SYNDROME

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AND
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This paper gives an account of 3 brothers all of whom have: (a) mental deficiency; (b) cerebellar signs; (c) absent tendon reflexes; (d) bilateral pes cavus and claw hands; (e) Charcot-Marie-Tooth distribution of wasting of all the limbs; (f) obesity of the trunk and face, and (g) premature arcus senilis.

The parents of the 3 brothers were first cousins. The father died from a coronary thrombosis. The mother is alive and well and states that she does not know of any relative of hers or of her late husband (apart from their 3 sons) who suffered from mental, nervous, or skeletal disease. They had one daughter, now aged 47, and four sons, of whom the second died at the age of 18 months (cause unknown). The daughter is married and has 2 daughters and neither she nor they have any neurologic, mental, or skeletal abnormality.

The remaining sons are all affected. Unsteadiness of gait was first noticed in J. when he was about two; in V. at about five, and in E. at seven years of age. In all three the condition came on gradually and slowly became worse until they were in their twenties, since when it has remained stationary.

J., aged 34, has a mental age of five; he has cerebellar signs as shown by rhythmic nystgamus on lateral deviation; dysarthria without any obvious lesion of the tongue, lips, or palate; ataxia and intention tremor of the limbs even with the eyes open. There is absence of all tendon reflexes. Bilateral marked pes cavus and claw hands (hyper-extension at the metacarpal-phalangeal joints and flexion deformity of the interphalangeal joints are present, with wasting of all limbs of characteristic Charcot-Marie-Tooth distribution, i.e., affecting the intrinsic muscles of the hands and feet, the lower third of the forearms, and the lower limbs extending up to lower third of the thighs. It is impossible to assess sensory disturbances because of the mental defect. The plantar reflexes are flexor. In addition to the neurologic signs there are marked obesity of the face and trunk; hypertension (blood pressure 180/120); supernummary digits on the hands and feet; marked arcus senilis; striae

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of abdomen and thighs, which, however, are not pigmented. He is not plethoric and his blood count, cerebrospinal fluid and Wassermann reactions are all normal.

V., age 41, has a mental age of five and the physical signs in his nervous system are identical with those of J. Though plump, he is not so obese as his brothers and is not hypertensive. He, also, has an arcus senilis, pes cavus, and claw hands.

E., age 37, has a mental age of 10 and his neurologic signs are identical with those found in J. and V. He has extreme obesity of the trunk, with a fat round face. His blood pressure is 210/130. He has glycosuria and a glucose tolerance curve shows that he is a moderately severe diabetic. He, also, has an arcus senilis, pes cavus, and claw hands.

Three papers which may have bearing on the subject are those by Roussy and Levy (13, 14, 15) who described 7 members of a family traced through four generations, all of whom had bilateral pes cavus, which was always the first sign; ataxia of the limbs of posterior column type; absent deep reflexes, but no cerebellar or pyramidal signs. After a time the condition did not progress. Three of their cases had slight wasting of the intrinsic muscles of the hands. Symonds and Shaw (18) described 10 members of a family in three generations all of whom had exactly the same signs as those described by Roussy and Levy, but 4 also had slight wasting of the hand muscles and one of them of the peronei. They considered the condition to be a forme fruste of Charcot-Marie-Tooth paralysis. Rombold and Riley (10) reported 8 members of a family afflicted in exactly the same way as the Roussy and Levy family, but they considered the disease to be a variant of Friedreich's ataxia. On the other hand, Popow (9) described 9 members of a family conforming to the Roussy and Levy description, and he agreed with them that this was a new syndrome (*la dystasie aréflexique héréditaire*). Spillane (16) reviewed the Roussy and Levy syndrome and added 21 cases from six generations of one family. Three of them also had a Charcot-Marie-Tooth distribution of muscle wasting. However, the 3 brothers described by us differ from the Roussy and Levy cases in that they all have cerebellar signs.

The association of cerebellar and probable posterior column signs in 3 brothers suggests Friedreich's ataxia. The finding of muscle wasting in patients with apparent Friedreich's ataxia has been described by Rook (11), Bramwell (3), Hodge (7), Whyte (20), Bing (2), Jendrassik (8), Spiller (17), Gordon (5), Greenfield (6), and also by Biemond (1). In a pathologic review of Friedreich's ataxia, Schub and Haymaker have reported degeneration of the anterior horn cells in some cases.

Moreover, Gallotti (4), Biemond (1), van Bogaert and Moreau (19), Ross (12) and also Spillane (16), have described cases in which a condition resembling Friedreich's ataxia has been associated with muscle wasting of the Charcot-Marie-Tooth distribution.

In none of the above-mentioned papers on either the Roussy and Levy syndrome or variants of Friedreich's ataxia is mental disturbance recorded except on three occasions but then only in isolated cases, but never as an hereditary or familial feature. The exception is the paper by Ross in which 2 brothers were mentally deficient. Association of these syndromes with obesity, hypertension, or premature arcus senilis has, as far as we are aware, not been recorded before.

The above family, the Huxley brothers, is described so that possibly they may throw light on the complex subject of the heredofamilial cerebellar ataxias.

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BAL THERAPY IN INFECTIOUS AND METABOLIC NEUROPATHIES

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The use of 2,3 dimercaptopropanol, known also as British Anti-Lewisite and "BAL" (7, 12) in severe acute neuropathies was reported in a recent communication (4). Additional cases have been studied to add an interval report on this therapeutic investigation.

The mechanism of the action of BAL is considered to be primarily a reactivation of sulfhydryl enzyme systems of the cells. Certain inorganic and organic substances, notably the heavy metals, arsenic, reactive organic halides, various oxidizing agents, quinones, and unsaturated ketones show a marked affinity for the sulfhydryl group of cellular proteins (3). Profound disturbances in cellular metabolism result from inactivation of these sulfhydryl enzymes. BAL, a synthetic derivative of propanol containing two sulfhydryl radicles, has a greater affinity than the enzymes for such sulfhydryl-utilizing substances. BAL removes these substances from the cell and proper enzymatic function is again possible (12, 1).

Since BAL has an affinity for metallic ions, it may also remove metals that ordinarily form an integral part of enzyme systems. Such metals as manganese, zinc, iron, copper, and magnesium are present in the prosthetic groups of enzymes. Removal of such metallic ions from the enzymes results in defective cellular metabolism. The toxic effects of BAL are considered to be due to such a mechanism (1, 13).

Ten new cases of peripheral neuropathy treated with BAL form the basis of this interval report. The etiologies were considered to be: dietary deficiency states in 4 cases, virus infections in 3 cases, cirrhosis of the liver in 2 cases, and diphtheria in one case.

At first impression, one would question how such diverse groups as deficiency states, toxic states, and virus infections could have a common therapeutic application. Yet on further analysis, a common denominator in these cases can be postulated, i.e., an underlying disruption of enzyme systems.

Four of the common vitamins, thiamine, riboflavin, nicotinamide,

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and pyridoxine, have been demonstrated to be precursors of substances which form prosthetic groups of important enzyme systems in the intermediate metabolism of many cells (5). Since enzymes are eventually destroyed during activity, there is a constant need for more of all enzymes (5). In deficiency states the failure to supply the vitamins results in defective enzyme formation and cellular dysfunction. When the neurone is the cell affected, a neuropathy results. Supplying the deficient vitamins will suffice in some cases to restore normal cellular function. But in many cases therapy with liver and vitamins does not result in return of enzyme formation. In some cases the neuropathy may even progress while under such replacement therapy (4). Evidently some metabolite is present to prevent utilization of the vitamins. Substances called antivitamins have been isolated which oppose the vitamins by destroying or neutralizing them or by successfully competing for their place in the cell substance (9). Such a mechanism could well explain the lack of response of the deficiency neuropathies to vitamin therapy. The action of BAL would then be a removal of the metabolite from the cell, presumably a sulfhydryl-utilizing substance.

A similar enzymatic disorder can be postulated if a virus is responsible for the infectious polyneuritis or Guillain-Barré disease. It is an accepted fact that viruses are obligatory intracellular organisms because they do not possess complete enzyme systems necessary for multiplication. The virus must utilize the enzyme systems of other cells to multiply (8). When the virus invades the peripheral neurone and annexes the enzymes the neurone itself needs for proper functioning, a neuropathy results. In these cases the most probable mechanism of BAL is the removal of metals from the prosthetic group of enzyme systems, which is enough to interfere with the multiplication of the virus, but not enough to disturb the function of the neurone. It is of particular interests that Rivers in discussing the treatment of virus diseases concludes: ". . . their (viruses) activities can be interfered with and their multiplication inhibited indirectly through the action of therapeutic agents which disturb enzyme systems and metabolic process of their host cells." He considered such a therapeutic approach as the practicable one to the problem.

The manner in which the diphtheria toxin disrupts neuronal function is not clear as yet. It is possible that the toxin has an affinity for sulfhydryl groups, for the administration of BAL produced a definite response in the case of this series. A similar explanation could be offered if the Guillain-Barré disease is due to a toxin as is suspected by some workers (8).

Results

In the evaluation of any therapy, it is difficult to assess the incidence of spontaneous recovery. One can but compare a group of similarly affected patients and judge the progress of the disease in each group. In the year preceding the use of BAL, patients who were treated with liver and vitamins alone took from two to four times as long to attain similar stages of recovery as those who received BAL as well. Spontaneous restoration of biochemical equilibrium occurs not infrequently but, in the writer's experience, the use of BAL results in a much higher incidence of such rapid recoveries.

Of the 10 cases which constitute the basis of this report, 7 were considered markedly improved during the period of BAL therapy which varied from one to four weeks. In the other 3 cases, the response was slight. In all 10 cases there was an improvement in the sensory sphere, particularly in the amelioration of the symptoms of hypersensitivity of the skin and muscles. In 2 cases it was evident from electrical tests that the changes in the motor neurone had proceeded to degeneration and BAL had no effect on the motor deficit. These cases show strikingly the different courses followed by cases still in the biochemical stage of neuronal dysfunction and by those in which neuronal damage had proceeded to degeneration. Comparing cases of similar degree of involvement, etiology, and duration, 3 cases of the biochemical group in which the lower limbs were completely paralyzed began to recover in the first week of therapy and were well in three, five, and six weeks, respectively. The infectious case where degeneration had occurred began to show motor recovery in the seventh month. In another comparison of cases with paralysis of the foot, motor recovery was essentially complete by the third, fourth, and sixth weeks in the biochemical group. In contrast, an analogous degenerative case had just begun to show motor recovery in the eighth month.

The BAL used in these cases consisted of a 10 per cent solution of 2,3 dimercaptopropanol with 20 per cent benzyl benzoate and peanut oil as the vehicle. The dosage may be calculated according to weight, the effective daily dose being from 1.5 to 3 mg. per kilogram. This is well below the toxic dose of the drug, which begins at 5 mg. per kilogram (6, 11). The writer has found it efficacious to use the routine dose of 200 mg. once daily, unless the patient is under 120 pounds. No reactions have yet been observed in the writer's cases to indicate the discontinuance of the drug. Aching in the limb or body occasionally occurs after an injection but this disappears in one half to one hour. Toxic symptoms with doses of 5 mg. per kilogram or higher have been de-

scribed as: pains and paresthesias in various parts of the body, perspiration and a feeling of warmth, lacrimation, salivation, blepharospasm, tremulousness, nausea, vomiting, restlessness, apprehension, severe malaise, and generalized weakness. These reactions are reported as lasting only from one to two hours (6, 11).

Three illustrative case reports follow. Case 1 represents a metabolic neuropathy occurring in a chronic deficiency state; case 2, an infectious polyneuritis and associated acute deficiency state; and case 3, a diphtheritic toxic neuropathy.

Case Reports

Case 1.—A 37 year old man had used alcohol excessively since the age of 20. In 1941 he had noted the sensation of pins and needles and hypersensitivity of the skin of his hands and lower limbs. In 1944 he began to have difficulty in walking and balancing and the skin of his limbs became numb and more hypersensitive. He considered his condition had been essentially stationary for the two years preceding admission.

Findings: On admission (Aug. 10, 1948) the physical examination was negative except for a severe glossitis. The blood showed an erythrocyte count of 5.85 million, 18 Gm. of Hb., and a hematocrit reading of 57. The gastric analysis and spinal fluid were within normal limits. The cephalin flocculation and thymol turbidity tests for liver function were normal on three occasions but the prothrombin time was 48 per cent on Sept. 9th and 60 per cent on Sept. 17th. The neurologic examination on Aug. 18th disclosed: inability to tandem walk or balance on one leg; a positive Romberg sign; ataxia of the heel-to-knee test; inability to stand on his heels because of motor weakness of the dorsiflexors of the ankle; mild weakness of extension of the ankle; paresthesias and dysesthesias from the hips and elbows distally; absent vibration sense below the rib cage; diminished deep pain appreciation in the Achilles tendons; impaired position sense in the toes and fingers; hypesthesia over the upper and lower whole extremities, with delayed conduction; absent deep tendon reflexes in the lower limbs.

Treatment: On Aug. 21st 2 cc. of BAL (200 mg.) and 2 cc. of crude liver extract (4 units) once a day were begun and continued through Sept. 7th. A total of 3.4 gm. of BAL was received over a 17 day period without any toxic symptoms. Examination on Sept. 8th showed that the patient had a much improved gait and co-ordination, the motor weaknesses were no longer apparent, the dysesthesias and sensory impairment had disappeared from the upper limbs and had greatly diminished in the lower limbs. Vibration sense was then present at the knees and the deep tendon reflexes were still absent in the lower extremities.

Case 2.—A 42 year old man noted in early April, 1948 numbness of the tips of his toes and soon afterward of both feet. At the same time the skin became so hypersensitive that he was unable to wear socks The hypersensitivity and numbness spread to the knees and into the finger tips during

the subsequent weeks. For three weeks prior to admission he had poor appetite, nausea, and vomiting.

Findings: On admission (May 18, 1948) the physical examination was negative except for a severe glossitis and a severe irritative sensory polyneuritis of the lower limbs. Free acid was present on gastric analysis. The erythrocyte count was 5.12 million and the Hb. 15.75 Gm. The bromsulfalein excretion, cephalin flocculation, and thymol turbidity tests showed normal liver function. The spinal fluid showed a mild protein increase, 57 mg. per cent and no cells.

Treatment: The regimen of 1.5 oz. of brewers' yeast, 100 mg. of thiamine chloride, and one ampoule of Soluble B* daily was begun on admission. The brewers' yeast was discontinued after three weeks. Two ampoules of Soluble B daily were given from May 27th to June 8th, then one ampoule again daily. A high protein, high vitamin diet was administered as is done to all deficiency cases. There was no improvement on such a regimen, in fact his neurologic status deteriorated. On July 23rd the neurologic examination revealed the following: moderate weakness of toe movements; mild weakness of finger, ankle, and knee movements; paresthesias, dysesthesias, and hyperesthesias in the hands and the whole lower limbs; diminished appreciation of pain and touch in stocking pattern below the mid calf; intact vibration and position sense; generalized hyper-reflexia with bilateral ankle clonus; and bilateral Babinski signs. All vitamin therapy was discontinued and from July 27th through August 3rd, BAL alone was given, in 100 mg. doses (1.5 mg. per kilogram) once daily. Examination on August 3rd showed a definite improvement in strength; normal sensation in the upper limbs; normal sensation except for some hyperesthesia below the mid calf in the lower limbs; a decrease of the hypertonicity of the muscles and a disappearance of the ankle clonus; bilateral Babinski signs.

Case 3.—A 50 year old man developed a severe sore throat on June 15, 1948. The diagnosis of diphtheria was established at another hospital. Tracheotomy was necessary and also treatment for cardiac failure. In early July he noted difficulty in eating, speaking, and swallowing and developed a paralysis of the right side of the face. Two weeks later he experienced numbness and burning of the hands and feet, and these sensory disturbances had progressed to the elbows and the knees at the time of the patient's transfer to the veterans' hospital.

Findings: On July 24th the physical examination was negative except for the nervous system. The urine showed a 2 plus albumin reaction. The spinal fluid and blood chemistry were normal. Only slight EKG changes were present on admission and two weeks later the EKG was normal. Neurologic examination on July 24th disclosed the following abnormalities: mild weakness of hand and foot movements; absent deep tendon reflexes in the upper and lower limbs; paresthesias and dysesthesias from the elbows

of calcium pantothenate, and 250 mg. of nicotinamide.

*Contains 10 mg. of thiamine, 10 mg. of riboflavin, 5 mg. of pyridoxine, 50 mg.

and knees distally; paralysis of the right facial and right pharyngeal muscles and of the right vocal cord; and a nasal twang to the voice.

Treatment: BAL was begun on July 24th, in doses of 125 mg. daily. Liver extract, 5 cc. (10 units) daily, was added on July 28th. During the first week of therapy there was a definite improvement in swallowing, the sensory symptoms had practically disappeared, and the power in the limbs increased to near normal. The response had been so satisfactory that the BAL was discontinued on Aug. 6th, and the liver stopped one week later. However, on Aug. 16th, weakness suddenly developed in the proximal muscles of the upper and lower limbs. BAL and liver extract, 1 cc. each daily, were resumed on Aug. 17th, but it was not until Aug. 21st that the progression of symptoms ceased. The skin and muscles of the legs and forearms had become hypersensitive again. The proximal arm muscles were so weak that the patient could not lift his arms, and the pelvic girdle muscles were similarly weak. In contrast, the distal muscle groups maintained good strength. In the second week of BAL and liver therapy the motor deficit began to resolve, and the BAL was discontinue on Sept. 2nd and the liver on Sept. 10th. By the middle of September, fair power against resistance was present in all affected muscles and the deep reflexes began to return in the arms. A month later there was no evidence of the previously severe neuropathy except for paresthesias in the toes and hypoactive deep tendon reflexes. The patient had received a total of 3.45 gm. of BAL in two courses of 15 and 17 days without any toxic symptoms, the second longest period of BAL administration in the series.

Comment

The mixed type of peripheral neuropathy, predominantly sensory, illustrated by Case 1, is the commonest seen in this clinic. The sensory disturbances have usually been present many months or years and the motor impairment ordinarily for a few weeks. The patient most often seeks medical aid after an exacerbation of sensory dysfunction or development of sufficient paralysis to prevent locomotion. These recent intensifications of symptoms are the first and most consistent signs to disappear during BAL therapy. The hypersensitivity of the muscles and skin begins to recede about the third or fourth day in most cases, and the motor dysfunction ameliorates around the end of the first week. The bulk of improvement tends to occur during the second week of therapy. Sometimes the long-standing paresthesias remain in the toes and are probably due to degenerative changes. The rapidly resolving symptoms are evidently biochemical disturbances, despite their long duration in some cases. Repeatedly it has been observed that neurologic dysfunction can exist for many months and still no changes of degeneration need occur. Such chronic biochemical disturbances could well explain why pathologic and clinical findings are sometimes seemingly

at a variance. The occurrence of symptoms of peripheral neuropathy in subacute combined degeneration of the cord is almost constant, yet actual degenerative changes are found in only about 5 to 20 per cent of cases (10. At present a pathologic method has not been devised to show such biochemical disturbances at necropsy, but perhaps the electron microscope and new biochemical techniques can furnish the solution.

Summary

It is suggested that the fundamental defect in peripheral neuropathies is an insufficient amount of enzymes for proper metabolism of the neurones. In cases of deficiency states, there is a defective formation of enzymes. In the infectious cases, the viruses deplete the supply of enzymes.

The suggested rationale for using BAL in neuropathies is: (a) in the metabolic type, to reactivate sulfhydryl enzyme systems where such sulfhydryl enzymes have been blocked by sulfhydryl-conjugating metabolites; (b) in the infectious type, to inhibit enzyme symptoms with metallic ions in prosthetic groups which are necessary for the metabolism of the viruses.

Biochemical disorders of the neurone may be of long duration and result in marked impairment of nerve function. Yet such disturbed physiology may be rectified and normal function may return in a few days or weeks with BAL therapy. In contrast, once degenerative changes occur, many months are required for regeneration of the neurone to attain similar return of function.

Ten new cases of metabolic and infectious peripheral neuropathy treated with BAL are summarized and 3 cases are reported in detail.

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RAPIDLY GROWING CARCINOMA OF THE LUNG AND PERFORATED DUODENAL ULCER IN A PATIENT TREATED WITH ELECTRIC SHOCK

NAOMI RASKIN, M.D.
AND
WILLIAM M. HULL, M.D.*

According to Selye (18), in patients under ACTH therapy, intense abdominal pain and exacerbation of pre-existing peptic ulcers may occur, presumably because ACTH stimulates the production of pepsin, gastric hydrochloric acid, and the total amount of gastric juice. Electroshock therapy (EST), which is a potent stress-producing factor, increases the patient's production of ACTH. Early (9) has reported that one EST has a greater action than 50 mg. of standard ACTH preparation. In patients with pre-existing duodenal ulcer, this increase may be sufficient to cause a perforation of the ulcer. The case reported seems to be of double interest, as carcinoma of the lung and perforated duodenal ulcer were discovered in the course of treatment.

Case Report

E. W., a 31-year-old single white woman was admitted to Boston State Hospital at the age of 20 because of her peculiar behavior, apprehension, anxiety, disheveled looks, filthy clothes, and rambling talk, the main topic of which was accusations against her family for maltreatment and against her father for physical maltreatment and incest.

The patient was the oldest of 9 siblings, 3 of whom were said to have died of neglect. Her mother was diabetic, her father a dull, clumsy individual whose maximum earnings were $20 a week. The mother's sister died in a state hospital; one brother was "very queer," another mentally defective. The paternal grandmother, with whom the family lived until her death, had a goiter and a difficult disposition. The family was notorious in the neighborhood for their filth and squalor. The S.P.C.C. agent stated that the children were like little animals and knew they were different from other children. Elizabeth was an outcast at school because of her offensive dirtiness. She felt the stigma and knew that she was looked down on. She wanted to improve her lot, and wanted friends, but her mother was lazy, sick, and careless, and she objected to Elizabeth's efforts, with the result that the girl took her clothes to a neighbor who showed her how to wash and mend them. She had a hard time at home. She became somewhat of a rebel and the mother used a stick on her, first alone, later with the help of

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her oldest son. Elizabeth was heard at night crying and screaming; she ran to neighbors for protection with her hair flying and her nose and hands bloody. She was sickly and undernourished, and lost much time at school because of illness. She did poorly in school work, was kept back, repeating the grades. The teachers noticed that she told little lies and stories that sounded queer, that dealt with things Elizabeth insisted were going on in her home. She began to tell neighbors that her father had relations with her, and that her mother knew about it but did nothing to stop it. She went to the police station, but she looked so queer and dirty and her talk was so rambling that nobody believed her story. She repeated, "I hate my mother," insisted she had been discriminated against by her family, starved and beaten, and said, "When people love you they are not supposed to hurt you." At the age of four, she had fallen and broken her nose. She had a plastic operation at the Massachusetts General Hospital at 16. Soon after this she began to complain of blanching of her feet and hands which otherwise were red and rough, of tiring easily, which prevented her from doing any work. She left school in the ninth grade and tried unsuccessfully to get a job, but never could keep one for more than a few days. She began to stay in bed till noon; she talked of suicide, of killing her family, of taking them to court for abuse, threatened to punish them for the way they had treated her all these years. The threats were never taken seriously by the family. The social service investigation by S.P.C.C. brought out that besides a wretched poverty, low mentality of both parents, filthiness, and neglect of the children, there was a marital friction, the father accusing his wife of having too many children and doing nothing to stop it. He wanted a separation from his wife and to have the children placed by social agencies. Elizabeth listened and kept washing her hands, saying she felt unclean. She accused her mother of having illegitimate children, her father of incest, and masturbated a great deal. She was obsessed with the idea of getting away from the filthy home, from the parents she hated, from the brood of unwashed, hungry, screaming brothers and sisters, but she never transformed the idea into action. Instead, she began wetting the bed, staying in the urine-soaked bed all day and hurling accusations against her father. At the insistence of the social agency she was taken to the Boston Psychopathic Hospital.

After six days' observation, she was transferred to Boston State Hospital with the diagnosis of psychosis with psychopathic personality.

On admission to Boston State Hospital, her physical examination was negative. Mental examination showed her to be excited but oriented.

Clinical Course. She was resentful, asocial, complaining, assaultive, difficult at all times, and bitter against her parents. She had insulin therapy from July 19, 1940 until September 29, 1940, without much benefit. She was allowed to go home on a trial visit, but soon had to be returned to the hospital. She deteriorated rapidly, was incontinent of urine, soiled herself, was denudative, and very destructive. Because of loss of weight, pallor and anemia, X-rays of the chest were taken repeatedly in 1941 and 1942, and

found negative. In 1945 and 1946 she again had numerous physical and laboratory examinations because an organic pathology was suspected. Severe secondary anemia was present in spite of a special nourishing diet. The red count was from 2.390.000 to 3.710.000 with Hg. from 43 to 45 per cent. Occult blood in the stool done once was negative. Gastric juice: hydrochloric acid was present but not increased. In 1946 she had a severe diarrhea of prolonged duration. No enteric pathogens were found in the culture of the stool. She was put on iron and liver extract and gained considerable weight, but her R.B.C. remained low. X-ray of the lungs showed no evidence of pulmonary tuberculosis. Flat abdominal X-ray revealed no abnormalities. G.I. series could not be done because the patient refused to co-operate. In 1951 it was decided to try EST. This treatment had been considered earlier but was postponed for a long time because of suspicion of organic lesion. Because of her violent, self-wearing behavior, negative laboratory findings except for consistent secondary anemia, no evidence of active pulmonary process by physical examination and by X-ray, and negative EKG, the patient was started on a course of EST on Aug. 24, 1951. She continued to be violently resistive for about three months, then gradually became frightened, whining, and whimpering. On December 21, 1951, after her 34th treatment, she had a sudden acute abdominal pain and vomiting. The temperature went up to 102. Physical examination showed tenderness in the right upper quadrant, fever, slight abdominal distention, and fluid in the left pleural cavity. On Dec. 23, 1951, 300 cc. of sterile, straw-colored fluid was removed. The cell count was 775 cells per 1 cm. with a predominance of lymphocytes. On Dec. 26, 1951, 2000 cc. of fluid was removed. The X-ray showed the heart and trachea deviated to the right. She was given procaine penicillin, 300,000 units daily and streptomycin. Chest-taps were repeatedly done. She began to expectorate blood-tinged sputum. In spite of the treatment, she went downhill and died Jan. 21, 1952, 35 days after the last EST.

Autopsy. Autopsy was performed 18 hours later. The body appeared fairly well nourished, but much older than her given age of 31. The vessels, including coronary arteries and aorta, were smooth. The pleura was very thick and shaggy, divided into separate compartments filled with fluid. The left lung was voluminous, held by firm adhesions, and was somewhat compressed by effusion in the left pleural cavity. Its surface was studded with tubercule-like lesions and the upper lobe contained a cavity filled with detritus and pus and communicating with the bronchus. Below the perforation, the bronchus was partially obstructed by a soft, flabby, white lesion. The peribronchial glands were numerous, large and white. The mediastinal glands were large and numerous. The right lung was congested and edematous, but free from lesions. The liver was large and heavy and on sectioning, was found to contain one large, round, white, soft nodule with several small ones in the right lobe. The spleen had numerous calcified round white nodules. The brain was edematous and soft, but had no gross lesions.

Gastro-intestinal tract: Esophagus negative. Stomach contained numer-

ous small submucosal hemorrhages. Rugae were well-pronounced and covered with a large amount of sticky mucous. A chain of large, white, rather soft lymph nodes outlined the lower curvature of the stomach. In the duodenum distal to the pylorus was a large ulcer measuring 4.5 x 3 cm., with firm, dark-red edges and a blood clot at the bottom. The base of the ulcer was adherent to the head of the pancreas. On the anterior surface of the first third of the duodenum was a large round opening with dark-red edges covered with thickened omentum. When the omentum was separated, the opening was found to measure 2 x 1.5 cm. and led into the ulcer.

Microscopic examination: Lungs showed a fast-growing, highly malignant, epithelial tumor, as evidenced by the polymorphism of its cells, numerous mitoses, and multinucleated cells. The tumor had involved the pleura, peribronchial glands, mediastinal glands, liver, omentum, lymphatic glands along both curvatures of the stomach and the serous coat of the duodenum. Sections of the duodenum showed a typical peptic ulcer. Brain sections showed no metastases. Pituitary gland showed an increase of eosinophilic cells; basophilic cells showed no Crooke's changes. Adrenal glands showed loss of cells in fasciculata. Metastases of the pulmonary carcinoma were found in the liver and in lymph nodes.

Discussion

Rokitansky (17) noticed that in cerebral lesions there often were changes in the gastric mucosa and perforations of the stomach which he ascribed to vagal disturbances. Brown-Sequard (6) described changes in the mucosa of the stomach following cerebral lesions. Burdenko and Mogilnitzki (7) produced small tuberal lesions in animals which were followed by gastric hemorrhages and erosions, acute ulcers, and occasionally by perforations. Beattie (4) noticed that direct stimulation of the tuber cinereum in animals was followed by hyperemia of the gastric mucosa. Watts and Fulton (23) noticed that the lesions of the hypothalamus affected the sympathetic innervation of the heart and intestinal tract in monkeys. Licht, Bishop, and Kendall (13) produced gastric lesions in rabbits by injection of small amounts of pilocarpine into the cerebrospinal fluid. Hoff and Sheehan (11) produced hemorrhagic erosions in the gastric mucosa in monkeys by experimental hypothalamic lesions. Nedzel (15) and Berg (5) produced gastric lesions in dogs by inducing vascular spasm with petressin. Keller (12) produced ulcerations in the digestive tract of the dog by vagotomy. In 1932 Cushing (8), in his paper entitled "Peptic Ulcer and Interbrain," described 11 cases, 3 of which ended in perforation. Cushing emphasized that erosions and ulcers in the gastrointestinal tract are not infrequently associated with various cerebral lesions and post-intracranial operation periods. Cushing postulated the existence of parasympathetic irritation or sympathetic paralysis of autonomic centers in the hypothalamus, which leads to

hypersecretion, hyperchlorhydria, hypermotility, and hypertonicity, especially marked in the pyloric segment. By the spasmodic contraction of the musculature, possibly accompanied by local spasms of the terminal blood vessels, small areas of ischemia or hemorrhagic infarcation are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperactive juices. Interbrain centers for vegetative impulses are easily affected by psychologic influences. Nervous people, through continuous worry and anxiety, may develop digestive disturbances comparable to those seen in experimental irritative lesions. Masten and Bunts (14) reported 6 cases of perforation of the stomach and esophagus in cerebral lesions and also mentioned the effect of pneumoencephalograms on these sympathetic and parasympathetic centers in the interbrain. Strassmann (21) described mucosal hemorrhages, ulcers, or softenings with perforations involving the esophagus, stomach, and duodenum, observed in association with various injuries and diseases of the meninges and brain in hundreds of cases.

Experimental, clinical, medical, and surgical observations have established definite relationship between interbrain lesions and lesions of the upper gastro-intestinal tract. Cushing had focused the attention on the relation of emotions, worry, and anxiety with digestive hyperacidity, often leading to ulcers. Selye (19) calls gastrointestinal ulcers "stress disease." The initial muscular contraction leading to the vascular spasm, local anoxemia of tissue, necrosis, ulceration, and digestion of tissue by the acid gastric juice can be brought about by nervous stimuli. Acute ulcers can rise in addition to and complicate other pathologic states, such as infections, meningitis, burns, "Curling ulcers," anaphylactic shock, intense emotional shock, and "air-raid ulcers." Personality structure accounts for the degree of the reaction to stress and much has been written about the type of person who is likely to develop an ulcer. The consensus is that frustration in an aggressive person lasting for a long time and presumably accompanied by intense autonomic discharge leads to hypermotility of gastric muscles, vascular constriction, and hypersecretion, i.e., to the factors responsible for the production of peptic ulcer. Ewalt (10) found hostility and anxiety in patients suffering from peptic ulcer and in patients with ulcer-like symptoms without mucosal erosions. This statement was confirmed by direct observation of the gastric or intestinal mucosa in fistulas by Wolf (24), which showed striking changes in the mucosa under emotional stimuli, especially hostility and resentment. The old observation of Rokitansky that peptic ulcers were associated with vagal disturbances was emphasized by Cushing who believed that direct stimulation of the vagal center or its descending fibers leads to hypersecretion, hypermotility, and hyper-

acidity. Alexander (1, 2), who devoted much time and study to the peptic ulcer patients, concluded that a conflict situation was operative in all cases regardless of the personality, with psychic stimuli from subconscious sources producing chronic excitation of the stomach comparable to the effect of organic lesions as described by Cushing and others, and thereby disturbing local gastric functions to the point of inducing gastric or duodenal ulcers. Relief of emotional states influences favorably the course of peptic ulcer. Emotional episodes tend to aggravate it. Barbiturates encourage healing by decreasing neurogenic and psychologic stress stimuli. According to Selye (18), treatment with large doses of ACTH and cortisone tends to aggravate the course of peptic ulcers and may even produce such lesions in previously healthy individuals. Administration of ACTH to a patient with a gastric ulcer may result in severe exacerbation of epigastric pain and tenderness. In shock there is endogenous ACTH discharge. In the patient subjected to the powerful, stress-producing action of EST, there is an increase of ACTH as revealed by 17-keto-steroids, lymphocytic and eosinophilic changes.

In our patient, who obviously did not benefit by EST, in whom hostility and anxiety remained unchanged, but in whom the EST had increased the production of pituitary hormones, the factors conducive to ulcer formation were increased in intensity and led to perforation of the ulcer with peritoneal reaction, but without peritonitis due to the protective adhesion of the omentum. The patient's clinical course from then on was accentuated by the presence of fluid in the left thoracic cavity. The patient was tapped several times, the fluid showed no tubercle bacilli on direct smear or in the culture. The X-rays taken after EST showed the presence of fluid and pulmonary findings consistent with atelectasis due to obstruction. The postmortem findings of the large tumor and numerous tubercle-like carcinomatous lesions of the lung with widespread metastases came as a surprise, as there was no clinical or radiologic evidence of the lung tumor prior to the EST. The type of the tumor cell was consistent with primary lung tumor, and numerous sections of the duodenal ulcer and of the stomach showed no malignant degeneration. The statistically unusual occurrence of carcinoma of the left lung in a 31 year old woman, its extent and rapid growth, raised the question of the relationship between its development and EST, which we are unable to answer.

ACTH has been used in large doses and found ineffective against cancer by Pearson (16), Taylor (22), Alpert (3), Spies (20), and others. Therefore, no benefit could be expected from much smaller doses of endogenous ACTH produced by EST. We venture a suggestion that EST increases the production of other hormones as well as

ACTH which may have a stimulating effect on the growth of the malignant cells.

Summary and Conclusions

A case is presented of a 31-year-old female schizophrenic who was treated with electric shock after eleven years of hospital residence, for the relief of her mental condition, and in whom a cancer of the left lung and a perforated duodenal ulcer were found at autopsy. The theories of the pathogenesis of the peptic ulcers are reviewed and the relationship between EST and perforation of the duodenal ulcer is discussed. The presence of a rapidly growing, malignant tumor of the lung posed the question of the possibility of the hypothalamic stimulation produced by EST and influencing the production of the hormone which had stimulated the growth of the malignant cells.

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SOCIETY PROCEEDINGS

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Meeting of November 30, 1953

Formation, Flow and Reabsorption of Cerebrospinal Fluid in Man.

William H. Sweet, M.D. and Herbert Locksley, M.D.*

On the basis of data obtained from multiple simultaneous isotopic tracer studies in man, including labeled water, various electrolytes and radioiodinated human serum albumin, we have been led to a theory of cerebrospinal fluid (CSF) formation, flow, and reabsorption which varies from current concepts. We have evidence that CSF is elaborated throughout the cerebrospinal fluid system independently of flow from one area to another. It is derived both from the choroid plexus in the ventricles and from structures bordering on the subarachnoid space. Furthermore, we have demonstrated that the reabsorption of water and electrolytes from the CSF occurs throughout the system independently of flow. These elements of the fluid enter and leave the subarachnoid space by direct molecular capillary exchange, and hence may be considered to be in a state of dynamic equilibrium with plasma, similar to that of other fluid components of the body.

The data presented tonight are derived mainly from 2 patients in whom we found it possible to isolate the lateral ventricles, on the one hand, from the subarachnoid space, on the other hand. In both patients, tumors filling the third ventricle had completely blocked CSF outflow from the large lateral ventricles over five years ago. At that time a Torkildsen type of ventriculocisternostomy was carried out.

The small plastic tube we used permitted CSF to bypass the block, and the intracranial pressures in both patients had remained essentially normal in the ensuing five years. We were now able to clamp the tube and preclude direct flow between ventricles and subarachnoidal space.

On the basis of studies in which we injected our isotopes either into the the blood stream or into the CSF compartments we concluded that (a) Water and electrolytes enter the CSF rapidly, both in the ventricles and throughout the subarachnoid space; the formation of the fluid is thus not an exclusive prerogative of the choroid plexus. (b) Water and electrolytes leave directly into the blood from both the ventricles and the subarachnoid space. (c) CSF does not suddenly come into being fully formed at any point with all its constituents in proper ratios, but each constituent is exchanging with blood at its own characteristic rate. (d) In contrast to

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water and electrolytes, protein is absorbed largely from the subarachnoid space, presumably from the arachnoidal villi. The site and rate of protein reabsorption are thus important determinants of the direction and rate of flow of CSF. (e) The net amount of CSF elaborated per day in the ventricles, over and above the large equivalent volume exchanged, is small.

Discussion.—Dr. James B. Ayer: I fear I am sadly out of date in the interpretation of spinal fluid production, flow, and absorption, using heavy water as index. Like most others I have accepted the conclusions of Dandy and Blackfan as to the choroidal origin of the cerebrospinal fluid. Although the presence of cerebrospinal fluid in the absence of choroidal plexus was thereby difficult to explain, Weed's postulate that some fluid is derived from pericellular and perivascular spaces was an acceptable explanation. There is highly suggestive evidence that the origin of hematogenous meningitis is primarily ventricular, i.e., that ventriculitis precedes meningitis, but this brings up the question of infection which is not the subject of tonight's discussion.

Dr. Wilfred Bloomberg: What consideration has been given to the basic situation that required the use of the Torkildsen tube in altering the hydrodynamic situation? I assume this occurred in cases of third ventricle tumor blocking the flow of spinal fluid. Would you comment on the pressure relationships that might have occurred in this situation and the effect they might have had?

Dr. Gilbert Horrax: I am speaking from the clinical situation. Two things: In the first place we have known for many years, in instances of hydrocephalus, that if you took out the choroid plexus, you would get a cessation of hydrocephalus. I wondered how he explains that. Second, in these patients with the tube, from a verified third ventricle tumor, is he sure there is no communication between lateral and fourth ventricle, because sometimes you do get a partial communication, and patients might live several years. Did they have X-ray treatment and thus let fluid through? Was there an actual block of the system?

Dr. Edgar A. Bering, Jr.: The estimation of the amount of cerebrospinal fluid produced by drainage is open to serious question. The amount of fluid produced is directly proportional to the pressure of the drainage system. This has been demonstrated in cats by Flexner, and I have found it to be true in patients on constant ventricular drainage.

What happens to the tracers in the cerebrospinal fluid after they reach equilibrium with the blood? Does the specific activity of the tracer in the cerebrospinal fluid fall with that in the blood?

Dr. Clemens E. Benda: Most of the younger people have grown up in the concept of Dandy and Weed on the production and circulation of the spinal fluid, which Dr. Selverstone even called the "classical" theory. It may be worth while to remember that the classical theory considered spinal fluid a very important medium of nutritional exchange, comparable to the lymph circulation in other body organs, and that most of the European schools of thought consider the spinal fluid not only as a mechanical water

jacket to protect the brain but think that the spinal fluid circulates through the brain parenchyma and is produced and absorbed through many different channels. Although the importance of the choroid plexus is not disputed, the choroid plexuses may well have an important regulatory function without being the sole source of production. In this country Hassin conducted, almost single-handed, a battle against the "classical" theory of Dandy and Weed, trying to demonstrate that the perivascular spaces had a great importance in the circulation of the spinal fluid and that some of the spinal fluid was produced through the vessel wall from the blood stream and was flowing toward the ventricular and subarachnoid spaces.

Actually the clinical experiences with hydrocephalus have shown that hydrocephalus cannot be explained merely through anomalies in the choroid plexus or anomalies of absorption through the meninges. Penfield, Hassin, and I showed in independent investigations that in the majority of cases of hydrocephalus a severe degeneration of the choroid plexus is present and no investigator has ever seen a hypertrophy of choroid plexuses which ought to be postulated if some of the previous authors were correct.

Dr. D. Denny-Brown: This reminds me of another session where our distinguished guest, Sir Geoffrey Jefferson, was present, and we discussed cerebral edema. After a long discussion he summarized the difficulty by saying: "I still don't understand where all this water in the brain comes from." With the old methods of study Weed showed that spinal fluid was being produced in large quantities by the choroid plexus, by blocking the pathways of absorption of spinal fluid with carbon particles. It seems to me that in some of Dr. Sweet's data, heavy water is behaving much the same as an electrolyte. We start by assuming that heavy water will behave as water. At the cistern the concentration curve shows a delayed component which suggests dilution. The question then is, what is diluting the heavy water? Is it choroid plexus fluid? That seems to be essence of this. Such a problem could only be solved by isolating either the ventricle or the spinal subarachnoid space.

Dr. Sweet: Does this isotope behave exactly the same as water?

Dr. Denny-Brown: That is the fundamental question.

Dr. Paul B. Jossmann: The differences of potassium concentration in the cisterna and the lumbar spaces may contribute to explain the development and course of familial periodic paralysis.

Dr. Donald D. Matson: From the clinical point of view, the interesting feature is the suggestion that the absorption of large molecules, that is, of protein, is a specific function of the arachnoid villi. It doesn't make any difference where all this water comes from. How it gets back into the blood stream is more important clinically. Unless cerebrospinal fluid can get to the arachnoid pathways and be absorbed normally, there, you are going to have hydrocephalus no matter at what rate the fluid is formed.

Dr. Herbert Locksley: The conclusions which Dr. Sweet has set forth tonight, despite their contradiction of classical theory, are entirely consistent with the excellent experimental data of workers such as Weed and

Dandy on which the theory is based. Before the present era of isotopic tracers, the technical problems of studying CSF under even approximately physiological conditions were almost insurmountable and ingenious non-physiologic tracers, such as ferricyanide and carbon black were used to follow the path of flow and reabsorption. It would seem that the classicists were tempted by their data into unsafe extrapolations. When it was demonstrated that CSF was formed by the choroid plexus, it was concluded that *all* the CSF was so formed; and when ferricyanide was consistently observed to find its way to the arachnoid villi, and that "plugging the pores" of the villi with carbon black granules produced hydrocephalus, it was concluded that *all* CSF was reabsorbed by this pathway. If our hypothesis regarding the arachnoid villi is correct, they play a specific role in reabsorbing certain large molecules and negatively charged particles such as protein and ferricyanide. However, to ascribe to them the entire role of reabsorption is as unreasonable as to say that all the interstitial fluid of the systemic capillary bed must return via the lymphatics. The other striking thing to us, was the dynamic nature of the relationship between CSF and plasma. With this concept the choroid plexus then ceased to be a CSF faucet and became a specialized capillary bed mediating fluid and electrolyte exchange approximately in accord with the rules of the general circulation. In the course of this exchange there is a certain amount of protein leakage across a very steep concentration gradient. Thus adequate conditions exist here also to apply Starling's theory of a dynamic balance between hydrostatic and osmotic forces. In this situation if protein is absorbed at a distance (arachnoid villi?), local accumulations of protein can produce local changes in pressure and impetus for flow and in the extreme condition of blockage, hydrocephalus. There may well be other factors contributing to flow such as a small "filtration pressure" across the barrier membrane (e.g., secretion) and tidal oscillations or pulsations associated with respiration and the cardiac cycle.

Dr. Sweet: One may ask how reasonable it is to draw conclusions with respect to normal mechanisms from these patients with tumor. We hope that neoplasms in a relatively static state for five years have modified the normal processes to a minimal degree. Dr. Horrax asked how we could be certain that there was no communication between the lateral and fourth ventricles. We determined this by injecting indigo carmine into the lateral ventricles in each patient. The dye stained the lumbar samples faintly only after several hours. This may possibly have been due to a slight leak along the Torkildsen tube between the ventricle and subarachnoid space. In any event we have this evidence that the block was nearly complete.

Anent the choroid plexuses, we do agree that they have a major function in exchanging electrolytes and water; this has long since been demonstrated by the fact that their removal arrests or improves hydrocephalus in many patients. Dr. Denny-Brown's question as to whether or not our tracer substances behave like the normal substances lies at the core of all tracer work. A discussion of it would take us a little far afield, but I may say that

we are planing to carry out comparative studies using HTO and D_2O since the heavy forms of water perhaps differ from each other and from their physiologic counterpart H_2O more than any of the other tracers used differs from its normal stable isotope. If the two forms of heavy water behave similarly, we should have more evidence that they, the labeled isotopes, are a valid mirror of the behavior of the substances present normally.

We should like to emphasize that the large volume of the ventricles in our patients resulted in a slower rate of change of concentration of tracer there than in the subarachnoid space for equal rates of passage of ions into each cubic centimeter of CSF. Thus in patient S.P. although after intra-arterial injection Cl^{38} was rising in concentration in the subarachnoid space as rapidly as in the lateral ventricles, the latter had about eight times the volume of the former. Hence Cl^{38} was entering into the lateral ventricles eight times as fast as into the subarachnoid space.

Dr. Jossmann commented on differences in potassium concentration; I should make it clear that the differences shown in our data refer only to labelled potassium, K^{42}, and are not intended to indicate the total content of concentration of physiologically effective potassium ions.

I should like to thank all of the discussors for their comments and searching questions.

Trigeminal Neurinomas. Prof. Sir Geoffrey Jefferson, F.R.S., M.S., F.R.C.S., F.R.C.P.

(No abstract of this paper is available.)

BOOK NOTES AND REVIEWS

Books received are acknowledged and given a brief description in this section. Selections serving a variety of interests will be made from these for a more extensive review, as far as space will allow.

BOOK NOTES

Abramson, Harold A., Editor: PROBLEMS OF CONSCIOUSNESS. [New York: Josiah Macy, Jr. Foundation, 1951. Pp. 178. $3.25.]

This slender volume is a verbatim account of the transactions of the Second Conference on Problems of Consciousness sponsored by the Josiah Macy, Jr. Foundation. At this meeting the disciplines of psychiatry, physiology, anthropology, psychology, sociology, zoology and religion were represented by well known authorities in these fields.

The report is a classical illustration of what occurs in cross-disciplinary discussions which at times appear to be little more than mental calisthenics. However, as an attempt to work out a technique of group communication and creativity such roundtable activities are well worthwhile and worth repeating for practice and improvement.

The discussions were centered about the three principal papers: "Consciousness, a Psychopathological and Psychodynamic View" by David Rapaport, "Variations in the Scope of Awareness" by Gregory Zilboorg and "Variations in States of Awareness in Schizophrenic Patients" by David G. Wright. All three of these papers as well as the associated discussions contained many valuable points of interest but very little was contributed to the understanding of consciousness.

Buros, Oscar K., Editor: THE FOURTH MENTAL MEASUREMENTS YEARBOOK. [Highland Park, New Jersey, 1953. The Gryphon Press. Pp. 1163. $18.00.]

The Fourth Yearbook presents the productive output in English speaking countries for 1948 through 1951, the volume supplementing earlier yearbooks. The material is given in two parts—the first part of the book lists the details concerning 793 tests and 596 original test reviews by various specialists. There are 53 extracts from reviews appearing in journals and 4,417 references on construction, use and limitations of various tests. In the second part tsere are 429 listed books on measurements and related fields and 758 extracts from books on statistical methods in education and psychological topics.

This gives some idea of the scope of this valuable book which as a whole is an extraordinary accomplishment. It should be available to

all psychologists and educators and at hand in the mental clinics to aid in appraisal of results where Rorschach, TAT, and other important tests are utilized daily.

Conn, Howard F., Editor: CURRENT THERAPY 1953: LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN: [Philadelphia, W. B. Saunders Co, 1953. Pp. 835. $11.00.]

This book like the previous volumes represents an outstanding achievement on the part of the editor, the large group of collaborators, and the publishers. In order to include all desirable material, it was necessary to make a rather large book that is best handled on a desk than in other common positions.

There are 16 sections, each dealing with a class of disorders according to organ systems with the exception of the last which contains the Appendices and Indices including a roster of drugs, table of metric and apothecaries systems and tables for preparing percentage solutions. Practically every type of therapy is covered for all varieties of human diseases and in addition preventive measures and surgical indications are emphasized when appropriate. These discussions on treatment are concise and easily followed with the two-column pages and a print especially suited to rapid reading.

The physician will find useful therapeutic information about practically every disorder that he is called upon to treat. The experience and opinions of many outstanding clinicians are at his service.

Kupper, William H.: DICTIONARY OF PSYCHIATRY AND PSYCHOLOGY. [Paterson, N. J. The Colt Press, 1953. Pp. 194. $4.50.]

The subtitle of this little book "An Illustrated Condensed Encyclopedia of Psychiatry, Neurology and Psychology" is rather accurately descriptive of the text which contains a truly large number of items and laconic definitions within the small space utilized. One finds illustrations of the anatomy of the nervous system, psychosomatic and neurologic terms, references for extended reading, lists of state hospitals for mental disorders, lists of psychiatric and psychologic journals, both American and foreign, historical items, brief biographical sketches of some of the leaders in the field and various other items not usually found in such a work, especially in a small book. For ready reference to unusual as well as the run of the psychiatric "mill" terms the volume should have a place in the psychiatrist's book shelf.

Patten, Bradley M.: HUMAN EMBRYOLOGY: SECOND EDITION. [New York and Toronto: The Blakiston Co., Inc., 1953. Pp. 798. 453 Illustrations and 2 Plates. $12.00.]

The standard of completeness characterizing the first edition of this excellent book has been maintained in terms of its basic organization and logical presentation. Although many parts of the book have not

been changed, extensive revisions have been made in the chapters dealing with the recent investigations on the early stages of human embryo development, on human implantation and on the development, of the heart and great vessels. A number of new illustrations have been added and some of the old ones omitted.

In this book one finds an excellent correlation of the development of the organ systems with postnatal structure and function such as an instructor needs for his purposes. The text contains most if not all of the useful information extant on human embryology and presents it in an easily readable style. There is an extensive classified bibliography and an adequate index.

Petrie, Asenath: PERSONALITY AND THE FRONTAL LOBES: AN INVESTIGATION OF THE PSYCHOLOGICAL EFFECTS OF DIFFERENT TYPES OF LEUCOTOMY. [Philadelphia: The Blakiston Company, 1952. Pp. 188: illustrated. $6.00.]

Over 50 patients who had been subjected to the operation of lobotomy were examined by the author at St. George's Hospital in London by the use of a series of psychological examinations. These tests were done on each patient previous to the operation and again 3 and 9 months postoperatively. All operations were performed by one surgeon, a standard bilateral closed incision in 27 cases, a rostrol open procedure in 15 and a unilateral operation in 8 cases. The patients selected were of high intelligence some having held professional or advanced business positions, were severely neurotic rather than psychotic in reaction type. Obsessions, anxieties, depressions and hysterical states were well represented, being the types that tended to afford reliable results from testing methods aimed at determining character and personality changes.

The testing methods are given in detail, as are the operative methods, statistical tables and examples of the responses to treatment. As usual, in such reports favorable results are emphasized but the author points out additional studies that should be made and recognizes the variety of individual responses that are possible in this field. The book is a valuable contribution to the field of psychology and psychosurgery.

Podalsky, Edward, Editor: ENCYCLOPEDIA OF ABERRATIONS. [New York: Philosophical Library, 1953. Pp. 550. $10.00.]

Although this volume is a useful one containing definitions, descriptions, and discussions of special topics by outstanding contributors in their various fields, the title of "Encyclopoedia" is an over statement since this implies a treatise more inclusive than the present one. While it does cover a large number of topics in psychiatry, it is definitely selective omitting practically all of the disorders associated with organic states excepting a few of the toxoemias. In other words, the book is not

a psychiatric dictionary, which it was obviously not intended to be, but is a compilation of definitions and articles arranged alphabetically for the convenience of the student of psychiatry and psychology. The sections on chronic alcoholism, epilepsy, crime, schizophrenia, and psychopathic personality among others are particularly informative.

NOTES AND NEWS

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